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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/170,344	03/30/94	KAST	W D45113TFM

EXAMINER
MINNIFIELD,N

ART UNIT | PAPER NUMBER
1813 | 13

18N1/0823

COOPER & DUNHAM
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

AUG 28 1995

DATE MAILED: 08/23/95

11/23/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 4-07-95 5-15-95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

RECEIVED
AUG 23 2004
OFFICE OF PETITIONS

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-2, 4-22, 24 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 3 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-2, 4-22, 24 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III DETAILED ACTION

Response to Amendment

15. Applicants' amendments filed April 17, 1995 and May 14, 1995 are acknowledged and have been entered. Claim 3 has been cancelled. Claims 1, 2, and 16-21 have been amended. Claims 1, 2, 4-22, and 24 are now pending in the present application. All prior rejections are withdrawn with the exception of those discussed below.

16. The text of the 35 U.S.C. Code not included in this Office Action can be found in the prior Office Action.

17. The information disclosure statement filed January 4, 1994 fails to comply with 37 CFR § 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicants state (April 17, 1995) that a substitute IDS will be filed, however it has not been received.

18. The objection to the specification and rejection of claims 1, 2, 4-22, and 24 under 35 U.S.C. § 112, first paragraph (i.e. lack of an enabling disclosure) is maintained. This rejection is maintained for essentially the same reasons as the rejection of claims 1-22 and 24 under this statutory provision, as set forth in paragraphs 17 and 18 of the last Office action. Applicants' arguments filed April 17,1995 have been fully considered but they are not deemed to be persuasive.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The disclosure is enabled for nonapeptide sequences from the E6 or E7 genes of HPV16 or HPV18, and MHC Class I molecules as specifically taught in the specification. The specification has not provided sufficient evidence of a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. Matlashewski et al. discloses that HPV18 proteins (E6 gene) maybe diagnostically useful since the proteins have been identified in specific human cancers, however the methods as claimed in this invention are not known in the art. Accordingly, amendment of the claims to what is supported in the specification or filing of evidence in the form of a Rule 132 declaration providing factual evidence supporting the broad range claims is suggested.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention.

Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Where the constitution and formula of a compound is stated only as probability and speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula. A disclosure involving a new chemical compound or composition must teach persons skilled in the art how to make the

compound. Incomplete teachings may not be completed by reference to subsequently filed applications.

The instant specification invites the skilled artisan to experiment. The factor which must be considered in determining undue experimentation are set forth in Ex parte Forman 230 USPQ 546. The factors include 1) quantity of experimentation necessary, 2) the amount of guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the predictability of the art and the 7) breath of the claims. With regard to factors three and six, it is noted that there are no working examples or support for in vivo efficacy of the active ingredients in a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition, or peptides from any HPV that bind to MHC Class I molecules. Such is not seen as sufficient to support the breath of the claims, wherein the scope of the claims encompasses how to prepare a peptide from any of the listed HPV proteins (or any other HPV protein) wherein the peptide binds to any human MHC Class I molecule. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves., see In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Applicants have argued that the specification is enabled and have cited Ruppert et al., Kast et al., Feltkamp et al., Vitiello et al., and Ressing et al. as support to demonstrate enablement, however it is noted that the specification must be enabled as of its filing date. Prior art references that were published after Applicants' effective filing date (5-5-92) cannot be used to rebut prima facie case of nonenablement under 35 USC 112. In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974).

Applicants have argued that it would be unethical to demonstrate HPV treatment in humans, however the Examiner has not suggested such a demonstration. Applicants have not demonstrated treatment of HPV in animal models. With regard

to the method of prophylactic or therapeutic treatment, it appears that the specification is a paper protocol. The specification does not show any therapy or prophylatic treatment, only in vitro studies; no animal studies using the peptides to demonstrate prophylatic or therapy treatment that would correlate to human efficacy have been set forth in the specification.

Applicants have argued that Kast et al. (1991, PNAS 88:2283-2287 and 1991, Immunol. Letters 30(2):229-232) show that one of skill in the art would readily understand from these references how to make and use the claimed invention. Kast et al. (1991, PNAS) disclose the immunization of synthetic peptides of Sendai virus, not HPV. Further, Kast et al. (1991, Immunol. Letters) does disclose the use of peptide vaccination, however the use of HPV peptides is not discussed. HPV is discussed with regard to using "... cultured human CTL for immunotherapy of virus-induced tumors" (p. 229). Furthermore, the reference discloses that there are several unanswered questions regarding peptide vaccination as a novel immnuotherapeutic or preventive approach in man (summary; p. 230, col. 2).

In response to Applicant's argument that Matlashewski et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides that bind in the groove on top of an MHC Class I molecule) are not stated in the claims. Therefore, it is irrelevant whether the reference includes those features or not.

19. The rejection of claims 1, 2, 4, 7, 8, 11, 13, and 15-23 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103 as obvious over Schoolnik et al. is maintained. This rejection is maintained for essentially the same reasons as the rejection of claims 1-22 and 24 under this statutory provision, as set forth in paragraph 24 of the last Office action. Applicants' arguments filed April 17, 1995 have been fully considered but they are not deemed to be persuasive.

Schoolnik et al. discloses synthetic peptides from HPV that are useful in the diagnosis and therapy of conditions associated with HPV infection (abstract; p. 9, l. 10-18; claims). Schoolnik et al. teaches the preparation of peptides from HPV16 (E6 and E7) or other HPV proteins useful to raise antibodies for diagnostic, protective (i.e. prophylactic), and therapeutic purposes and vaccines, as well as various mode of administration (p. 3, l. 1-39; p. 5, l. 28-50; p. 4, l. 27 to p. 5, l. 24; p. 7, l. 47 to p. 8, l. 8).

It is noted that the claims recite a peptide comprising an amino acid sequence from a protein of E6 or E7 of HPV 16 or HPV 18.

The teachings of Schoolnik et al. anticipates the claimed invention by disclosing a peptide from a HPV protein wherein the peptide binds to a MHC Class I molecule, and a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. The compositions and methods disclosed in Schoolnik et al. are believed to inherently possess properties which anticipates the claimed invention or if they are not the same the composition and methods, the HPV peptides (and compositions) and methods of treatment as disclosed by Schoolnik et al. would none the less render the claims obvious because it possesses the components necessary to prepare a peptide from HPV and methods of treatment as claimed in the instant application. Binding of MHC Class I molecules via T-cell activation is an inherent part of the process of generating an immunogenic response in a mammal. Since the Office does not have the facilities for examining and comparing applicants' method for preparation of a HPV peptide and methods of treatment of the prior art, the burden is on applicant to show a novel or unobvious differences between the claimed product and the product of the prior art (i.e., that the peptide, composition, and method of use of the prior art does not possess the same material structural and functional characteristics of the claimed composition and methods of preparation).

See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

In response to Applicant's argument that Schoolnik et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides have to fit snugly in the groove of HLA Class I molecule; pockets in the groove; specific anchor residues) are not stated in the claims. Therefore, it is irrelevant whether the reference includes those features or not.

It is noted that the use of prior art published after Applicants' effective filing date can not be used rebut rejections.

20. The following new rejection has not been necessitated by the amendment.

21. Claims 5, 6, 8, 10, 12, and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

22. No claims are allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is (703) 305-3394. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christine M. Nucker, can be reached on (703) 308-4028. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield
August 21, 1995

HAZEL F. SIDBERRY
PRIMARY EXAMINER
GROUP 1800

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP–APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER	
NOTICE OF REFERENCES CITED	8/170344	1813		13
	APPLICANT(S) Kast et al.			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R	Kast et al. 1991. Improved efficacy of a virus-derived peptide ... Immunol. Lett. 30 229-232
S	Kast et al. 1991. Protection against lethal Sendai virus infection by ... PNAS 88 2283-2287.
T	
U	

EXAMINER	DATE	
[signature]	8/21/95	

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

Form PTO 948 (Rev. 10-93) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 8/170344

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftpersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date) 3/30/94, are
A. ___ not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.
B. ✓ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink. Color.
   ___ Not black solid lines. Fig(s)_____
   ___ Color drawings are not acceptable until petition is granted.

2. PHOTOGRAPHS. 37 CFR 1.84(b)
   ___ Photographs are not acceptable until petition is granted.

3. GRAPHIC FORMS. 37 CFR 1.84 (d)
   ___ Chemical or mathematical formula not labeled as separate figure. Fig(s)_____
   ___ Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis. Fig(s)_____
   ___ Individuals waveform not identified with a separate letter designation adjacent to the vertical axis. Fig(s) _____

4. TYPE OF PAPER. 37 CFR 1.84(e)
   ___ Paper not flexible, strong, white, smooth, nonshiny, and durable. Sheet(s)_____
   ___ Erasures, alterations, overwritings, interlineations, cracks, creases, and folds not allowed. Sheet(s)_____

5. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable paper sizes
   21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)
   21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)
   21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)
   21.0 cm. by 29.7 cm. (DIN size A4)
   ___ All drawing sheets not the same size. Sheet(s)_____
   ___ Drawing sheet not an acceptable size. Sheet(s)_____

6. MARGINS. 37 CFR 1.84(g): Acceptable margins:

Paper size			
21.6 cm. X 35.6 cm. (8 1/2 X 14 inches)	21.6 cm X 33.1 cm. (8 1/2 X 13 inches)	21 cm. X 27.9 cm (8 1/2 X 11 inches)	21 cm X 29.7 cm (DIN Size A4)
T 5.1 cm. (2")	2.5 cm. (1")	2.5 cm. (1")	2.5cm
L .64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	2.5 cm
R .64 cm. (1/4")	.64 cm (1/4")	.64 cm. (1/4")	1.5 cm
B .64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.0 cm

   Margins do not conform to chart above.
   Sheet(s)_____
   ___Top (T) ___ Left (L) ___Right (R) ___ Bottom (B)

7. VIEWS. 37 CFR 1.84(h)
   REMINDER: Specification may require revision to correspond to drawing changes.
   ___ All views not grouped together. Fig(s)_____
   ___ Views connected by projection lines. Fig(s)_____
   ___ Views contain center lines. Fig(s)_____

Partial views. 37 CFR 1.84(h)(2)
   ___ Separate sheets not linked edge to edge. Fig(s)_____
   ___ View and enlarged view not labeled separately. Fig(s)_____
   ___ Long view relationship between different parts not clear and unambiguous. 37 CFR 1.84(h)(2)(ii) Fig(s)_____

Sectional views. 37 CFR 1.84(h)(3)
   ___ Hatching not indicated for sectional portions of an object. Fig(s)_____
   ___ Hatching of regularly spaced oblique parallel lines not spaced sufficiently. Fig(s)_____
   ___ Hatching not at substantial angle to surrounding axes or principal lines. Fig(s)_____
   ___ Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s)_____
   ___ Hatching of juxtaposed different elements not angled in a different way. Fig(s)_____

Alternate position. 37 CFR 1.84(h)(4)
   ___ A separate view required for a moved position. Fig(s)_____

Modified forms. 37 CFR 1.84(h)(5)
   ___ Modified forms of construction must be shown in separate views. Fig(s)_____

8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   View placed upon another view or within outline of another. Fig(s)_____
   Words do not appear in a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s)_____

9. SCALE. 37 CFR 1.84(k)
   Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s)_____
   ___ Indication such as "actual size" or "scale 1/2" not permitted. Fig(s)_____
   ___ Elements of same view not in proportion to each other. Fig(s)_____

10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
   ___ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings). Fig(s)_____

11. SHADING. 37 CFR 1.84(m)
   ___ Shading used for other than shape of spherical, cylindrical, and conical elements of an object, or for flat parts. Fig(s)_____
   ___ Solid black shading areas not permitted. Fig(s)_____

12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
   ___ Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(1) Fig(s) 1-2
   ___ Numbers and reference characters used in conjuction with brackets, inverted commas, or enclosed within outlines. 37 CFR 1.84(p)(1) Fig(s)_____
   ___ Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(1) Fig(s)_____
   ___ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s)_____
   ___ Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s)_____

13. LEAD LINES. 37 CFR 1.84(q)
   ___ Lead lines cross each other. Fig(s)_____
   ___ Lead lines missing. Fig(s)_____
   ___ Lead lines not as short as possible. Fig(s)_____

14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
   ___ Number appears in top margin. Fig(s) 1-3
   ___ Number not larger than reference characters. Fig(s)_____
   ___ Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s)_____

15. NUMBER OF VIEWS. 37 CFR 1.84(u)
   ___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s)_____
   ___ View numbers not preceded by the abbreviation Fig. Fig(s)_____
   ___ Single view contains a view number and the abbreviation Fig.
   ___ Numbers not larger than reference characters. Fig(s)_____.

16. CORRECTIONS. 37 CFR 1.84(w)
   Corrections not durable and permanent. Fig(s)_____.

17. DESIGN DRAWING. 37 CFR 1.152
   Surface shading shown not appropriate. Fig(s)_____
   ___ Solid black shading not used for color contrast. Fig(s)_____

Descriptive matters chg (Fig 1-3)

ATTACHMENT TO PAPER NO. _____ REVIEWER _____ DATE 6/8/94

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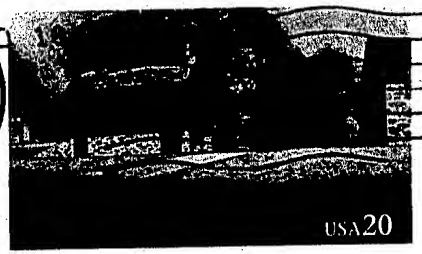
03/06/96 NO UA NO.GMF 2280 1



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COOPER & DUNHAM

1185 AVENUE OF THE AMERICAS

NEW YORK, N.Y. 10036

Applicant Wybe Martin Kast et al - Client No. 2805

Client Vereenigde File No. 45113 Atty. TFM

Date February 23, 1996

Kindly acknowledge receipt of the accompanying

AMENDMENT (O.A. 8/23/95)
Certificate of Mailing

Petition Under 37 C.F.R. 1.136(a)
Check for $ 900.00 for three month extension

Serial No. 08/170,344
Due: February 23, 1996

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by placing your receiving date stamp hereon and returning to us.

ocket No	45113	Application #	08/170344
ountry	United States	Application Dt	04JA1994
ase Type	REGULAR CASE TYPE	Patent No	
elation Type	ORIGINAL OR PATENT CASE	Grant Dt	
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iling No		Publication Dt	
ttorney	ROBERT D. KATZ	Assigned	
gent		Expiration Dt	
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arent No	PCT/NL93/00093	Update Dt	06JL2004
arent Grant Dt		Update Tm	0928
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Act Due Date	04SE1994	Resp Atty #1	
Taken Dt		Resp Atty #2	
DeadLn Dt			
Action	10mo FOREIGN FILING REMINDE	Comp Dt	
Act Due Date	04NO1994	Resp Atty #1	
Taken Dt		Resp Atty #2	
DeadLn Dt			
Action	11mo FOREIGN FILING REMINDER	Comp Dt	
Act Due Date	04DE1994	Resp Atty #1	
Taken Dt		Resp Atty #2	
DeadLn Dt			
Action	12mo FOREIGN FILING DEADLINE	Comp Dt	
Act Due Date	04JA1995	Resp Atty #1	
Taken Dt		Resp Atty #2	
DeadLn Dt			
Action	6 MONTH RESPONSE DUE	Comp Dt	
Act Due Date	04AP1995	Resp Atty #1	
Taken Dt	04AP1995	Resp Atty #2	
DeadLn Dt			
Action	3 MONTH RESPONSE DUE	Comp Dt	
Act Due Date	23NO1995	Resp Atty #1	
Taken Dt	23FE1996	Resp Atty #2	
DeadLn Dt			
Action	6 MONTH RESPONSE DUE	Comp Dt	
Act Due Date	23FE1996	Resp Atty #1	
Taken Dt	23FE1996	Resp Atty #2	
DeadLn Dt			
Action	STATUS INQUIRY DUE	Comp Dt	
Act Due Date	28NO2004	Resp Atty #1	
Taken Dt	18JE2004	Resp Atty #2	
DeadLn Dt			
Action	PETITION TO REVIVE DUE	Comp Dt	
Act Due Date		Resp Atty #1	
Taken Dt	28MY2004	Resp Atty #2	
DeadLn Dt			

Inventors

v Name MARTIN WYBE KAST Assigned

Title

tle
:PTIDES OF HUMAN PAPILLOMA VIRUS

CLIENT NO 2805

FILE NO. 45113

Ser. No.

APPLICATION OF

WYBE MARTIN KAST
CORNELIS JOSEPH MARIA MELIEF
ALESSANDRO D. SETTE
JOHN C. SIDNEY

FOR

PEPTIDES OF HUMAN PAPILLOMA VIRUS FOR USE IN HUMAN T CELL RESPONSE INDUCING COMPOSITIONS

Filed MARCH 30, 1994 Ser. No. 07/170,344

File No. 45113 Client

Executed

Date

at

N. P.

REMARKS

CORRES. TO INT'L APPLN. NO. PCT/NL93/00093 FILED 4 MAY 1993

ENTIRE interest assigned MARCH 17 1994 to RIJKSUNIVERSITEIT LEIDEN

Recorded MARCH 30 1994 Reel 7001 Frame 669

COOPER & DUNHAM
30 ROCKEFELLER PLAZA, NEW YORK, N.Y. 10112

Appn. Ser. No. | Inventor: | Patent No.

FILE NO. 45113

VEREENIGDE

CONFIRMATION COPY

OCTROOIBUREAUX

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Ir H.A. Witmans
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*trade marks and designs

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Mr P.A. van der Wees

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Arnhem
Ir C.M. Jansen

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in association with
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1185 Avenue of the Americas
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Attn. Mr. Thomas F. Moran

BY FACSIMILE
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Den Haag (The Netherlands)
Nieuwe Parklaan 97

December 10, 1997

Your ref. 45113
Our ref. Ren/92028-310

Re: U.S. patent application Serial No. 08/170,344
"Peptides of Human Papilloma Virus for use in Human T Cell Response Inducing Compositions" - Wijbe Martin Kast et al.

Dear Mr. Moran,

In the matter of the above-identified patent application I kindly request you to send me a copy of the current claims.

Thanking you in advance for your assistance.

Very truly yours,
VEREENIGDE OCTROOIBUREAUX

on behalf of
J. Renes

NvM

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RDK

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Attn. Mr. Thomas F. Moran

BY FACSIMILE
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Den Haag (The Netherlands),
Nieuwe Parklaan 97

January 27, 1998

Your ref. 45113
Our ref. Ren/92028-310

Re: U.S. patent application Serial No. 08/170,344
"Peptides of Human Papilloma Virus for use in Human T Cell Response Inducing Compositions" - Wijbe Martin Kast et al.

Dear Mr. Moran,

With reference to my letter of December 10, 1997 I kindly request you to send me a copy of the current claims in the above-referenced application by return.

Thanking you in advance for your assistance.

Very truly yours,
VEREENIGDE OCTROOIBUREAUX

J. Renes

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January 28, 1998

BY FACSIMILE
Dr. J. Renes
Vereenigde Octrooibureaux
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2508 DH The Hague
Netherlands

Re: Your Ref. Ren/92028-310 - Wybe Martin Kast et al
Peptides of Human Papilloma Virus for Use in
Human T Cell Response Inducing Compositions
Serial No. 08/170,344 filed March 30, 1994
Our Docket 45113

Dear Dr. Renes:

In response to your letter of December 10, 1997, attached please find a retyped version of the pending claims as amended. Please send all further correspondence in this matter to me. Mr. Moran has retired from the practice of law. I look forward to working with you on this matter.

Very truly yours,

Robert D. Katz

RDK:lg
Enclosure

CLAIMS AS OF 1/28/98

25. (Rewritten, canceled claim 1) A peptide comprising an amino acid sequence derived from protein of human papilloma virus (HPV), wherein said amino acid sequence comprises a nonapeptide derived from protein E6 or E7 of HPV 16 or HPV 18 and wherein said nonapeptide has the ability to bind in the grooves on top of the human major histocompactability complex (MHC) Class I molecule.

2. A peptide according to claim 25, wherein said amino acid sequence is a nonapeptide.

4. A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1.

5. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
KLPQLCTEL (residues 18-26 of HPV16 protein E6) SEQ ID NO:2
QLCTELQTT (residues 21-29 of HPV16 protein E6) SEQ ID NO:3
LCTELQTTI (residues 22-30 of HPV16 protein E6) SEQ ID NO:4
ELQTTIHDI (residues 25-33 of HPV16 protein E6) SEQ ID NO:5
LQTTIHDII (residues 26-34 of HPV16 protein E6) SEQ ID NO:6
TIHDIILEC (residues 29-37 of HPV16 protein E6) SEQ ID NO:7
IHDIILECV (residues 30-38 of HPV16 protein E6) SEQ ID NO:8
CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
FAFRDLCIV (residues 52-60 of HPV16 protein E6) SEQ ID NO:10
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
PLCDLLIRC (residues 102-110 of HPV16 protein E6) SEQ ID NO:12
TLHEYMLDL (residues 7-15 of HPV16 protein E7) SEQ ID NO:13
YMLDLQPET (residues 11-19 of HPV16 protein E7) SEQ ID NO:14
MLDLQPETT (residues 12-20 of HPV16 protein E7) SEQ ID NO:15
RLCVQSTHV (residues 66-74 of HPV16 protein E7) SEQ ID NO:16
TLEDLLMGT (residues 78-86 of HPV16 protein E7) SEQ ID NO:17
LLMGTLGIV (residues 82-90 of HPV16 protein E7) SEQ ID NO:18
GTLGIVCPI (residues 85-93 of HPV16 protein E7) SEQ ID NO:19 and
TLGIVCPIC (residues 86-94 of HPV16 protein E7) SEQ ID NO:20

a fragment, homolog, isoform, derivative, genetic variant and conservative variant of any one of these amino acid sequences which has the ability to bind to human MHC Class I allele HLA-A2.1.

6. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV18, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1 and is selected from the group consisting of:

KLPDLCTEL (residues 13-21 of HPV18 protein E6) SEQ ID NO:21
SLQDIEITC (residues 24-32 of HPV18 protein E6) SEQ ID NO:22

LQDIEITCV (residues 25-33 of HPV18 protein E6) SEQ ID NO:23
EITCVYCKT (residues 29-37 of HPV18 protein E6) SEQ ID NO:24
KTVLELTEV (residues 36-44 of HPV18 protein E6) SEQ ID NO:25
ELTEVFEFA (residues 40-48 of HPV18 protein E6) SEQ ID NO:26
FAFKDLFVV (residues 47-55 of HPV18 protein E6) SEQ ID NO:27
DTLEKLTNT (residues 88-96 of HPV18 protein E6) SEQ ID NO:28
LTNTGLYNL (residues 93-101 of HPV18 protein E6) SEQ ID NO:29
TLQDIVLHL (residues 7-15 of HPV18 protein E7) SEQ ID NO:30
FQQLFLNTL (residues 86-94 of HPV18 protein E7) SEQ ID NO:31
QLFLNTLSF (residues 88-96 of HPV18 protein E7) SEQ ID NO:32
LFLNTLSFV (residues 89-97 of HPV18 protein E7) SEQ ID NO:33 and
LSFVCPWCA (residues 94-102 of HPV18 protein E7) SEQ ID NO:34, and

a fragment, homolog, isoform, derivative, genetic variant and conservative variant of any one of these amino acid sequences which has the ability to bind to human MHC Class I allele HLA-A2.1.

7. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class 1 allele HLA-A1.

8. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 and E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A1 and is selected from the group consisting of:

YRDGNPYAV (residues 61-69 of HPV16 protein E6) SEQ ID NO:35
WTGRCMSCC (residues 139-147 of HPV16 protein E6) SEQ ID NO:36
MSCCRSSRT (residues 144-152 of HPV16 protein E6) SEQ ID NO:37
TTDLYCYEQ (residues 19-27 of HPV16 protein E7) SEQ ID NO:38
EIDGPAGQA (residues 37-45 of HPV16 protein E7) SEQ ID NO:39 and
HVDIRTLED (residues 73-81 of HPV16 protein E7), SEQ ID NO:40, and

a fragment, homolog, isoform, derivative, genetic variant and conservative variant of any one of these amino acid sequences which has the ability to bind to human MHC Class I allele HLA-A1.

9. A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A3.2.

10. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A3.2 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
IILECVYCK (residues 33-41 of HPV16 protein E6) SEQ ID NO:41
CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO:42
QQLLRREVY (residues 42-50 of HPV16 protein E6) SEQ ID NO:43
IVYRDGNPY (residues 59-67 of HPV16 protein E6) SEQ ID NO:44
YAVCDKCLK (residues 67-75 of HPV16 protein E6) SEQ ID NO:45

AVCDKCLKF (residues 68-76 of HPV16 protein E6) SEQ ID NO:46
VCDKCLKFY (residues 69-77 of HPV16 protein E6) SEQ ID NO:47
KFYSKISEY (residues 75-83 of HPV16 protein E6) SEQ ID NO:48
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
ISEYRHYCY (residues 80-88 of HPV16 protein E6) SEQ ID NO:49
RHYCYSLYG (residues 84-92 of HPV16 protein E6) SEQ ID NO:50
SLYGTTLEQ (residues 89-97 of HPV16 protein E6) SEQ ID NO:51
TTLEQQYNK (residues 93-101 of HPV16 protein E6) SEQ ID NO:52
QQYNKPLCD (residues 97-105 of HPV16 protein E6) SEQ ID NO:53
LIRCINCQK (residues 107-115 of HPV16 protein E6) SEQ ID NO:54
HLDKKQRFH (residues 125-133 of HPV16 protein E6) SEQ ID NO:55
CMSCCRSSR (residues 143-151 of HPV16 protein E6) SEQ ID NO:56
SCCRSSRTR (residues 145-153 of HPV16 protein E6) SEQ ID NO:57
CCRSSRTRR (residues 146-154 of HPV16 protein E6) SEQ ID NO:58
HYNIVTFCC (residues 51-59 of HPV16 protein E7) SEQ ID NO:59
YNIVTFCCK (residues 52-60 of HPV16 protein E7) SEQ ID NO:60
CCKCDSTLR (residues 58-66 of HPV16 protein E7) SEQ ID NO:61 and
KCDSTLRLC (residues 60-68 of HPV16 protein E7) SEQ ID NO:62,
and

a fragment, homolog, isoform, derivative, genetic variant and conservative variant of any one of these amino acid sequences which has the ability to bind to human MHC Class I allele HLA-A3.2.

11. A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-All.2.

12. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-All.2 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
IILECVYCK (residues 33-41 of HPV16 protein E6) SEQ ID NO:41
CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO:42
QQLLRREVY (residues 42-50 of HPV16 protein E6) SEQ ID NO:43
IVYRDGNPY (residues 59-67 of HPV16 protein E6) SEQ ID NO:44
YAVCDKCLK (residues 67-75 of HPV16 protein E6) SEQ ID NO:45
AVCDKCLKF (residues 68-76 of HPV16 protein E6) SEQ ID NO:46
VCDKCLKFY (residues 69-77 of HPV16 protein E6) SEQ ID NO:47
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
ISEYRHYCY (residues 80-88 of HPV16 protein E6) SEQ ID NO:49
LIRCINCQK (residues 107-115 of HPV16 protein E6) SEQ ID NO:54
TGRCMSCCR (residues 140-148 of HPV16 protein E6) SEQ ID NO:63
CMSCCRSSR (residues 143-151 of HPV16 protein E6) SEQ ID NO:56
SCCRSSRTR (residues 145-153 of HPV16 protein E6) SEQ ID NO:57
HYNIVTFCC (residues 51-59 of HPV16 protein E7) SEQ ID NO:59
YNIVTFCCK (residues 52-60 of HPV16 protein E7) SEQ ID NO:60
CCKCDSTLR (residues 58-66 of HPV16 protein E7) SEQ ID NO:61and

VCPICSQKP (residues 90-98 of HPV16 protein E7), SEQ ID NO:64
and

a fragment, homolog, isoform, derivative, genetic variant and conservative variant of any one of these amino acid sequences which has the ability to bind to human MHC Class I allele HLA-All.2.

13. A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A24.

14. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A24 and is selected from the group consisting of:

MHQKRTAMF (residues 1-9 of HPV16 protein E6) SEQ ID NO:65
LQTTIHDII (residues 26-34 of HPV16 protein E6) SEQ ID NO:6
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO:42
LLRREVYDF (residues 44-52 of HPV16 protein E6) SEQ ID NO:66
VYDFAFRDL (residues 49-57 of HPV16 protein E6) SEQ ID NO:67
PYAVCDKCL (residues 66-74 of HPV16 protein E6) SEQ ID NO:68
KCLKFYSKI (residues 72-80 of HPV16 protein E6) SEQ ID NO:69
EYRHYCYSL (residues 82-90 of HPV16 protein E6) SEQ ID NO:70
HYCYSLYGT (residues 85-93 of HPV16 protein E6) SEQ ID NO:71
CYSLYGTTL (residues 87-95 of HPV16 protein E6) SEQ ID NO:72
RFHNIRGRW (residues 131-139 of HPV16 protein E6) SEQ ID NO:73 and
RAHYNIVTF (residues 49-57 of HPV16 protein E7), SEQ ID NO:74,
and

a fragment, homolog, isoform, derivative, genetic variant and conservative variant of any one of these amino acid sequences which has the ability to bind to human MHC Class I allele HLA-A24.

15. A peptide according to claim 25, having a length of from 9 to 12 amino acids.

16. A pharmaceutical composition containing a prophylactically or therapeutically effective amount for eliciting cellular immune response of a peptide according to claim 25, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

17. A pharmaceutical composition containing a prophylactically or therapeutically effective amount for eliciting cellular immune response of a peptide according to claim 25 which is capable of inducing a T cell response effective against HPV, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

18. A pharmaceutical composition containing a prophylactically or therapeutically effective amount for eliciting cellular immune response of a peptide according to claim 25 for inducing a HLA Class I-restricted $CD8^+$ cytotoxic T cell response effective against HPV, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

Den Haag • Groningen • Arnhem • [redacted]rtogenbosch • Amersfoort • Nijmegen

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Your ref. 45113
Our ref. ME/P20884US00

Den Haag,
January 20, 2004

Re.: Patent Application in the U.S. of America No. 08/170,344
for
of RIJKSUNIVERSITEIT LEIDEN

Could you please supply us with a status report of the above mentioned application as we have not heard from you since January 28,1998.

Yours faithfully,
VEREENIGDE

Rozendaal

Records Department
A. Rozendaal

V313.1

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/170,344	03/30/94	KAST	W D45113TFM

EXAMINER	
MINNIFIELD,N	
ART UNIT	**PAPER NUMBER**
1802	16

18M1/0614

COOPER & DUNHAM
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

DATE MAILED: 06/14/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 2-26-96.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 2, 4-18, 25 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 2, 4-18, 25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

Part III DETAILED ACTION

Response to Amendment

15. Applicants' amendment filed February 26, 1996 is acknowledged and has been entered. Claims 1, 19-22, and 24 have been cancelled. Claims 2-8 and 10-18 have been amended. New claim 25 has been added. Claims 2, 4-18, and 25 are now pending in the present application. All prior rejections are withdrawn with the exception of those discussed below.

16. The text of the 35 U.S.C. Code not included in this Office Action can be found in the prior Office Action.

17. The information disclosure statement filed January 4, 1994 fails to comply with 37 CFR § 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicants state (April 17, 1995) that a substitute IDS will be filed, however it has not been received.

The present amendment filed (2-26-96) directed the Examiner to the April 7, 1995 amendment with respect to the content and relevance of the publications referred to in the IDS. The IDS references that have not been considered are EP0375555 and EP0456197. Applicants have not provided an english translation nor a statement of content and relevance of these references in any of the amendments. These references have not been considered as to the merits.

18. The objection to the specification and rejection of claims 2, 4-18 (and now claim 25) under 35 U.S.C. § 112, first paragraph (i.e. lack of an enabling disclosure) is maintained.

This rejection is maintained for essentially the same reasons as the rejection of claims 1-22 and 24 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The disclosure is enabled for nonapeptide sequences from the E6 or E7 genes of HPV16 or HPV18, and MHC Class I molecules as specifically taught in the specification. The specification has not provided sufficient evidence of a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. Matlashewski et al. discloses that HPV18 proteins (E6 gene) maybe diagnostically useful since the proteins have been identified in specific human cancers, however the methods as claimed in this invention are not known in the art. Accordingly, amendment of the claims to what is supported in the specification or filing of evidence in the form of a Rule 132 declaration providing factual evidence supporting the broad range claims is suggested.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention.

Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Where the constitution and formula of a compound is stated only as probability and speculation, the disclosure is not sufficient to support claims identifying the compound by

such composition or formula. A disclosure involving a new chemical compound or composition must teach persons skilled in the art how to make the compound. Incomplete teachings may not be completed by reference to subsequently filed applications.

The instant specification invites the skilled artisan to experiment. The factor which must be considered in determining undue experimentation are set forth in Ex parte Forman 230 USPQ 546. The factors include 1) quantity of experimentation necessary, 2) the amount of guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the predictability of the art and the 7) breath of the claims. With regard to factors three and six, it is noted that there are no working examples or support for in vivo efficacy of the active ingredients in a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition, or peptides from any HPV that bind to MHC Class I molecules. Such is not seen as sufficient to support the breath of the claims, wherein the scope of the claims encompasses how to prepare a peptide from any of the listed HPV proteins (or any other HPV protein) wherein the peptide binds to any human MHC Class I molecule. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves., see In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Applicants have argued that the specification is enabled and have cited Ruppert et al., Kast et al., Feltkamp et al., Vitiello et al., and Ressing et al. as support to demonstrate enablement, however it is noted that the specification must be enabled as of its filing date. Prior art references that were published after Applicants' effective filing date (5-5-92) cannot be used to rebut prima facie case of nonenablement under 35 USC 112. In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974).

Applicants have argued that it would be unethical to demonstrate HPV treatment in humans, however the Examiner has not suggested such a demonstration. Applicants have not demonstrated treatment of HPV in animal models. With regard to the method of

prophylactic or therapeutic treatment, it appears that the specification is a paper protocol. The specification does not show any therapy or prophylactic treatment, only in vitro studies; no animal studies using the peptides to demonstrate prophylactic or therapy treatment that would correlate to human efficacy have been set forth in the specification.

Applicants have argued that Kast et al. (1991, PNAS 88:2283-2287 and 1991, Immunol. Letters 30(2):229-232) show that one of skill in the art would readily understand from these references how to make and use the claimed invention. Kast et al. (1991, PNAS) disclose the immunization of synthetic peptides of Sendai virus, not HPV. Further, Kast et al. (1991, Immunol. Letters) does disclose the use of peptide vaccination, however the use of HPV peptides is not discussed. HPV is discussed with regard to using "... cultured human CTL for immunotherapy of virus-induced tumors" (p. 229). Furthermore, the reference discloses that there are several unanswered questions regarding peptide vaccination as a novel immunotherapeutic or preventive approach in man (summary; p. 230, col. 2).

In response to Applicant's argument that Matlashewski et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides that bind in the groove on top of an MHC Class I molecule) are not stated in the claims. Therefore, it is irrelevant whether the reference includes those features or not.

Applicant's arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Applicants have asserted that as the methods claims directed to methods of prophylactic or therapy treatment of a human have been cancelled that this objection should be eliminated. However, claims (16-18) directed a pharmaceutical composition containing a prophylactically or therapeutically effective amount for eliciting cellular immune response of a peptide and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant are not enabled for the same reasons as methods claims. The claims as presently written indicate or suggest that the 'pharmaceutical composition' would be administered to an animal or human,

however the specification is not enabled for such administration as previously indicated. Further, such short peptides require immunogenic carriers to ensure an immune response.

The claims also recite fragments, homologs, isoforms, derivatives genetic variants or conservative variants of the amino acid sequences and that these fragments, homologs, isoforms, derivatives genetic variants or conservative variants of the amino acid sequences will bind to the grooves on top of the MHC Class I molecule. The specification discloses that variants and derivatives include any amino acid substitution, deletion, or other processes (p. 17). Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (Bowie et al. 1990; p. 1306; p. 1308) and is well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in protein and the result of such modifications is unpredictable based on the instant disclosure.

The specification does not support the broad scope of the claims which encompass all variants of the protein because the specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants, if any, can be made which retain the biological activity of the intact protein; and the specification provide essentially no guidance as to which

of the essentially infinite possible choices is likely to be successful. Further, Houghten et al. teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore effect antibody production (p. 21) as well as antibody binding. Houghten et al. also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection." and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al. teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the derivatives that retain immunodominant regions and immunological activity if the regions have been altered.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions encompassing a variant, fragment, derivatives, homologs, isoforms etc as presently claimed. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the protein structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed peptides, for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species which could not be distinguished without undue experimentation. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

19. Claims 12 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

This rejection is maintained. It is noted that Applicants attempted to amend these claims with regard to the Markush language, however the instruction for the amendment of these claims is unclear. The line numbers stated in the amendment filed February 26, 1996 are not the same as those in the amendment filed July 18, 1994.

20. The rejection of claims 2, 4, 7, 8, 11, 13, and 15-18 (and now 25) under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103 as obvious over Schoolnik et al. is maintained. This rejection is maintained for essentially the same reasons as the rejection of claims 1, 2, 4, 7, 8, 11, 13, and 15-22 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Schoolnik et al. discloses synthetic peptides from HPV that are useful in the diagnosis and therapy of conditions associated with HPV infection (abstract; p. 9, l. 10-18; claims). Schoolnik et al. teaches the preparation of peptides from HPV16 (E6 and E7) or other HPV proteins useful to raise antibodies for diagnostic, protective (i.e. prophylactic), and therapeutic purposes and vaccines, as well as various mode of administration (p. 3, l. 1-39; p. 5, l. 28-50; p. 4, l. 27 to p. 5, l. 24; p. 7, l. 47 to p. 8, l. 8).

It is noted that the claims recite a peptide comprising an amino acid sequence from a protein of E6 or E7 of HPV 16 or HPV 18.

The teachings of Schoolnik et al. anticipates the claimed invention by disclosing a peptide from a HPV protein wherein the peptide binds to a MHC Class I molecule, and a

method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. The compositions and methods disclosed in Schoolnik et al. are believed to inherently possess properties which anticipates the claimed invention or if they are not the same the composition and methods, the HPV peptides (and compositions) and methods of treatment as disclosed by Schoolnik et al. would none the less render the claims obvious because it possesses the components necessary to prepare a peptide from HPV and methods of treatment as claimed in the instant application. Binding of MHC Class I molecules via T-cell activation is an inherent part of the process of generating an immunogenic response in a mammal. Since the Office does not have the facilities for examining and comparing applicants' method for preparation of a HPV peptide and methods of treatment of the prior art, the burden is on applicant to show a novel or unobvious differences between the claimed product and the product of the prior art (i.e., that the peptide, composition, and method of use of the prior art does not possess the same material structural and functional characteristics of the claimed composition and methods of preparation). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

In response to Applicant's argument that Schoolnik et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides have to fit snugly in the groove of HLA Class I molecule; pockets in the groove; specific anchor residues) are not stated in the claims. Therefore, it is irrelevant whether the reference includes those features or not.

It is noted that the use of prior art published after Applicants' effective filing date can not be used rebut rejections.

Applicant's arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Applicants' comments have been addressed previously. Applicants directed the Examiner to the previous response. It is noted at p. 11 of the previous response that

Applicants stated "... one was demonstrated by applicants not to have the binding ability to HLA molecule which is a prerequisite to be a CTL epitope...". Evidence to support Applicants' assertion that the prior art does not anticipated or obviate the claimed invention should be submitted in the form of a declaration.

21. The following new rejection has not been necessitated by the amendment.

22. Claims 2, 4-18 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 and its dependent claims are vague and indefinite in the recitation of "comprising" as the use of the open-ended term "comprises" which fails to exclude unrecited steps and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). Claim 25 is directed to a peptide comprising an amino acid sequence derived from a HPV protein wherein the sequence comprises a nonapeptide from E6 or E7 of HPV 16 or HPV 18. Claim 9 is indefinite and lacks proper antecedent basis in that the claim depends from claim 1 which has been cancelled.

23. No claims are allowed.

24. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT

MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is (703) 305-3394. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield
May 31, 1996

James C. Housel
JAMES C. HOUSEL 6/10/96
SUPERVISORY PATENT EXAMINER
GROUP 180

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER	
NOTICE OF REFERENCES CITED	8/170344	1802		16
	APPLICANT(S) KAST ETAL.			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
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FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	R	Bowie et al. 1990. Science 247: 1306-1310.
	S	Houghten et al. 1986. Vaccines 86 pp. 21-25.
	T	

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MESSAGE:

I enclose the Office Action finally rejecting the application in connection with U.S. Application No. 08/170,344, filed March 30, 1994 (your ref. no. ME/P20884US00). Please send me instructions on how to respond and we will file a response along with a petition to revive the application.

As mentioned we will also need a Terminal Disclaimer, which we can send to you for signature by your client.

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Part III DETAILED ACTION

Response to Amendment

15. Applicants' amendment filed February 26, 1996 is acknowledged and has been entered. Claims 1, 19-22, and 24 have been cancelled. Claims 2-8 and 10-18 have been amended. New claim 25 has been added. Claims 2, 4-18, and 25 are now pending in the present application. All prior rejections are withdrawn with the exception of those discussed below.

16. The text of the 35 U.S.C. Code not included in this Office Action can be found in the prior Office Action.

17. The information disclosure statement filed January 4, 1994 fails to comply with 37 CFR § 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicants state (April 17, 1995) that a substitute IDS will be filed, however it has not been received.

The present amendment filed (2-26-96) directed the Examiner to the April 7, 1995 amendment with respect to the content and relevance of the publications referred to in the IDS. The IDS references that have not been considered are EP0375555 and EP0456197. Applicants have not provided an english translation nor a statement of content and relevance of these references in any of the amendments. These references have not been considered as to the merits.

18. The objection to the specification and rejection of claims 2, 4-18 (and now claim 25) under 35 U.S.C. § 112, first paragraph (i.e. lack of an enabling disclosure) is maintained.

This rejection is maintained for essentially the same reasons as the rejection of claims 1-22 and 24 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The disclosure is enabled for nonapeptide sequences from the E6 or E7 genes of HPV16 or HPV18, and MHC Class I molecules as specifically taught in the specification. The specification has not provided sufficient evidence of a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. Matlashewski et al. discloses that HPV18 proteins (E6 gene) maybe diagnostically useful since the proteins have been identified in specific human cancers, however the methods as claimed in this invention are not known in the art. Accordingly, amendment of the claims to what is supported in the specification or filing of evidence in the form of a Rule 132 declaration providing factual evidence supporting the broad range claims is suggested.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention.

Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Where the constitution and formula of a compound is stated only as probability and speculation, the disclosure is not sufficient to support claims identifying the compound by

such composition or formula. A disclosure involving a new chemical compound or composition must teach persons skilled in the art how to make the compound. Incomplete teachings may not be completed by reference to subsequently filed applications.

The instant specification invites the skilled artisan to experiment. The factor which must be considered in determining undue experimentation are set forth in Ex parte Forman 230 USPQ 546. The factors include 1) quantity of experimentation necessary, 2) the amount of guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the predictability of the art and the 7) breath of the claims. With regard to factors three and six, it is noted that there are no working examples or support for in vivo efficacy of the active ingredients in a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition, or peptides from any HPV that bind to MHC Class I molecules. Such is not seen as sufficient to support the breath of the claims, wherein the scope of the claims encompasses how to prepare a peptide from any of the listed HPV proteins (or any other HPV protein) wherein the peptide binds to any human MHC Class I molecule. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves., see In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Applicants have argued that the specification is enabled and have cited Ruppert et al., Kast et al., Feltkamp et al., Vitiello et al., and Ressing et al. as support to demonstrate enablement, however it is noted that the specification must be enabled as of its filing date. Prior art references that were published after Applicants' effective filing date (5-5-92) cannot be used to rebut prima facie case of nonenablement under 35 USC 112. In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974).

Applicants have argued that it would be unethical to demonstrate HPV treatment in humans, however the Examiner has not suggested such a demonstration. Applicants have not demonstrated treatment of HPV in animal models. With regard to the method of

prophylactic or therapeutic treatment, it appears that the specification is a paper protocol. The specification does not show any therapy or prophylactic treatment, only in vitro studies; no animal studies using the peptides to demonstrate prophylactic or therapy treatment that would correlate to human efficacy have been set forth in the specification.

Applicants have argued that Kast et al. (1991, PNAS 88:2283-2287 and 1991, Immunol. Letters 30(2):229-232) show that one of skill in the art would readily understand from these references how to make and use the claimed invention. Kast et al. (1991, PNAS) disclose the immunization of synthetic peptides of Sendai virus, not HPV. Further, Kast et al. (1991, Immunol. Letters) does disclose the use of peptide vaccination, however the use of HPV peptides is not discussed. HPV is discussed with regard to using "... cultured human CTL for immunotherapy of virus-induced tumors" (p. 229). Furthermore, the reference discloses that there are several unanswered questions regarding peptide vaccination as a novel immunotherapeutic or preventive approach in man (summary; p. 230, col. 2).

In response to Applicant's argument that Matlashewski et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides that bind in the groove on top of an MHC Class I molecule) are not stated in the claims. Therefore, it is irrelevant whether the reference includes these features or not.

Applicant's arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Applicants have asserted that as the methods claims directed to methods of prophylactic or therapy treatment of a human have been cancelled that this objection should be eliminated. However, claims (16-18) directed a pharmaceutical composition containing a prophylactically or therapeutically effective amount for eliciting cellular immune response of a peptide and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant are not enabled for the same reasons as methods claims. The claims as presently written indicate or suggest that the 'pharmaceutical composition' would be administered to an animal or human,

however the specification is not enabled for such administration as previously indicated. Further, such short peptides require immunogenic carriers to ensure an immune response.

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This rejection is maintained. It is noted that Applicants attempted to amend these claims with regard to the Markush language, however the instruction for the amendment of these claims is unclear. The line numbers stated in the amendment filed February 26, 1996 are not the same as those in the amendment filed July 18, 1994.

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23. No claims are allowed.

24. Applicant's amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield
May 31, 1996

James C. Housel 6/10/96
JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER
GROUP 180

TO SEPARATE, HOLD [redacted] AND BOTTOM EDGES, SNAP-APART AND DISC[redacted]D CARBON

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	8/170344	1802	16
	APPLICANT(S) KAST ETAL.		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R Bowie et al. 1990. Science 247: 1306-1310.

S Houghten et al. 1986. Vaccines 86 pp. 21-25.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/170,344	03/30/94	KAST W	D45113TFM

EXAMINER: MINNIFIELD, N

18M1/0614

COOPER & DUNHAM
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

ART UNIT	PAPER NUMBER
1802	16

DATE MAILED: 06/14/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 2-26-96.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.**

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 2, 4-18, 25 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 2, 4-18, 25 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

* U.S. GPO: 1995-409-290/40029

08/230344

Briefed in 180

NL93|00093

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INITIALS

ABANDONED [redacted]

Date Entered or Counted			Date Received or Mailed
	1.	Application papers.	RECEIVED JUN 14 1994 GROUP 1800
	2.	Declaration	30 Nov 1994
	3.	105	04 April 1994
	4.	PCT/…	02 MAY 1994
	5.	Pre. No. Corf	5/17/94
	6.	Prel. Amdt / A	
	7.	Response …	
	8.	1 …	10-… 10/3
	9.	Raw Sequence Listing (OK)	9/6/94
	10.	Rej. Time 3 mos	4/7/95
	11.	Amdt C	7/7/95
	12.	Suppl. Response	3/15/95
	13.	Rejection 3 mos	8-03-95 8/21
	14.	Ext. (3)	2-26-96
	15.	Amdt D	2-26-96 2/23
	16.	F Rej 3 mos	6-14-96 6/10
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	18.	Power to Insp.	3/10/04
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Confirmation Report – Memory Send

Page : 001
Date & Time: Mar-17-04 15:25
Line 1 : +212 391 0525
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Machine ID : cooper&dunham

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Date	:	Mar-17 15:21
To	:	☎01131704166799
Number of pages	:	015
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End time	:	Mar-17 15:25
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COOPER & DUNHAM LLP
1185 Avenue of the Americas, New York, New York 10036

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PLEASE DELIVER THE FOLLOWING PAGES

TO	:	Dr. J. Renes
COMPANY	:	Vereenigde Octrooibureaux
FAX NO.	:	011-31-70-416-6799
FROM	:	Robert D. Katz, Esq.

TOTAL NUMBER OF PAGES, INCLUDING COVER PAGE: 15

DATE : March 17, 2004

X CONFIDENTIAL X URGENT

If this facsimile message has reached you in error, please notify us by collect telephone and return it by the Postal Service, as it may contain attorney privileged and confidential information.

MESSAGE:

I enclose the Office Action finally rejecting the application in connection with U.S. Application No. 08/170,344, filed March 30, 1994 (your ref. no. ME/P20884US00). Please send me instructions on how to respond and we will file a response along with a petition to revive the application.

As mentioned we will also need a Terminal Disclaimer, which we can send to you for signature by your client.

IF YOU DO NOT RECEIVE ALL OF THE PAGES, PLEASE CALL SHAKINAH DAVIS AS SOON AS POSSIBLE AT (212) 278-0459.

Shakinah Davis

From: Shakinah Davis
Sent: Monday, March 29, 2004 2:57 PM
To: 'j.renes@vereenigde.nl'
Subject: REMINDER Correspondence from Robert D. Katz

Dear Dr. Renes:

We forwarded the Office Action for U.S. Application No. 08/170,344 (your ref. no. ME/P20884US00; our ref. no. 45113) on March 17, 2004. Please let us know at your earliest convenience how we should proceed.

Robert D. Katz
(c/o Assistant, Shakinah Davis)
COOPER & DUNHAM LLP
1185 Avenue of the Americas
New York, New York 10036
Tel. (212) 278-0400
Fax.(212) 391-0525

Robert D. Katz

From: Einerhand M. [m.einerhand@vereenigde.nl]
Sent: Thursday, May 13, 2004 11:18 AM
To: Aude Gerspacher
Cc: Robert D. Katz; Elst van der N.
Subject: RE: FW: your ref 45113 our ref ME -20884us00

Dear Bob,

I have just been in contact with the client to inquire about the timing of the response. The situation at this moment is that the licensee has not yet responded. The client assumes that it will not be before next week before we will be able to provide you with instructions.

I discussed the case with a US-agent who also does work for us. He mentioned that there is also a possibility to revive abandoned applications when the abandonment is unavoidable. He suggested that in that case there would be no need to file a terminal disclaimer. What do you think about this opportunity? Is it possible to request revival under this regime in the present case?

Sincerely,

Mark Einerhand

-----Original Message-----
From: KATZ22@aol.com [mailto:KATZ22@aol.com]
Sent: vrijdag 7 mei 2004 15:45
To: m.einerhand@vereenigde.nl
Subject: Re: FW: your ref 45113 our ref ME -20884us00

Mark--Yes, next week will be in time. Please forward to agerspacher@cooperdunham.com, with a copy to me at , and we will get it filed as soon as possible. Thanks. Have a good weekend. Bob

"MMS <unipat>" made the following annotations.

13-05-2004, 17:20:06
****
All incoming and outgoing email is scanned to protect against viruses and other malicious content.
****

Shakinah Davis

From: Aude Gerspacher
Sent: Friday, May 14, 2004 10:51 AM
To: 'Einerhand M.'
Cc: Robert D. Katz
Subject: RE: FW: your ref 45113 our ref ME -20884us00

Dear Mark:

Thank you for your e-mail. As far as the timing of filing the petition, the U.S. Patent office requires that once an application becomes inadvertently abandoned, the applicant must act with diligence. The standard for diligence at the Patent Office is one of "reasonable diligence", which "does not require that applicant or his attorney ... drop all other work and concentrate on the particular invention involved". We will file the petition as soon as we receive your instructions.

In addition, there is a provision in the rules for reviving applications for which abandonment was unavoidable. 37 C.F.R 1.137(a) provides that if the delay was *unavoidable*, a petition may be filed to revive the application. Such a petition requires a) the reply required (i.e. the response to the outstanding office action); b)the petition fee; c) a *showing* that the delay was unavoidable; and 4) a Terminal Disclaimer. There is an express requirement for a Terminal Disclaimer. The requirements for filing a petition under this section are actually more stringent as a *showing* (i.e. facts and evidence) must be submitted and be to the satisfaction of the Director reviewing the petition. All that is required for a petition to revive *unintentionally* abandoned applications is a statement asserting the delay was unintentional. In addition, the U.S. Patent Office Manual of Patent Examination Procedures warns that a petition filed for unavoidable delay has less chance of being granted and will inevitably take more time for a decision to be made due to the more stringent "unavoidable" standard. [MPEP 711.03(c)]

I hope this answers your questions and addresses your concerns. Please feel free to contact me if you have additional questions.

Best regards,
Aude

Aude Gerspacher, Esq.
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, NY 10036
Tel: 212-278-0506
Fax: 212-391-0525

-----Original Message-----
From: Einerhand M. [mailto:m.einerhand@vereenigde.nl]
Sent: Thursday, May 13, 2004 11:18 AM

[redacted]

To: Aude Gerspacher
Cc: Robert D. Katz; Elst van der N.
Subject: RE: FW: your ref 45113 our ref ME -20884us00

Dear Bob,
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I discussed the case with a US-agent who also does work for us. He mentioned that there is also a possibility to revive abandoned applications when the abandonment is unavoidable. He suggested that in that case there would be no need to file a terminal disclaimer. What do you think about this opportunity? Is it possible to request revival under this regime in the present case?
Sincerely,
Mark Einerhand

-----Original Message-----
From: KATZ22@aol.com [mailto:KATZ22@aol.com]
Sent: vrijdag 7 mei 2004 15:45
To: m.einerhand@vereenigde.nl
Subject: Re: FW: your ref 45113 our ref ME -20884us00

Mark--Yes, next week will be in time. Please forward to agerspacher@cooperdunham.com, with a copy to me at , and we will get it filed as soon as possible. Thanks. Have a good weekend. Bob

"MMS <unipat>" made the following annotations.

13-05-2004, 17:20:06
****
All incoming and outgoing email is scanned to protect against viruses and other malicious content.
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RDK

Den Haag • Groningen • Arnhem • 's-Hertogenbosch • Amersfoort • Nijmegen

Patent Attorneys
Trademark Attorneys
Attorneys-at-Law

VEREENIGDE

BY FACSIMILE: +1 212 391 0525
Cooper & Dunham
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Confirmation Copy

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e-mail patent@vereenigde.nl
trademark@vereenigde.nl
legal@vereenigde.nl

www.vereenigde.com

Your ref. 45113
Our ref. ME/P20884US00

Den Haag,
June 1, 2004

Re: U.S. patent application No. 08/170,344
in the name of Rijksuniversiteit Leiden

Dear dr. Katz,

The client has approved the draft petition to revive that you provided for their review. Please go forward and file the petition. The signing of the terminal disclaimer by the University will take some time. We will forward you the signed disclaimer upon receipt thereof by us. As discussed on the phone, you will file the petition with an unsigned disclaimer, together with a letter explaining that we will file the signed disclaimer as soon as we have the signatures.

On a different note, the client has requested that we forward a letter to you. The letter, of which a copy is herein enclosed, is self-explanatory.

Sincerely,
VEREENIGDE

M. Einerhand

ne

SEED CAPITAL INVESTMENTS

Vereenigde
T.a.v. de heer dr M.P.W. Einerhand
Snouckaertlaan 42
3811 MB AMERSFOORT

per fax: 033 422 7319
confirmation by post

S294.04d /Your ref. ME/P20884US00 / HPV-V US Patent Application No. 08/170,334
18 May 2004

Dear Mr. Einerhand,

We recently received your letter dated 29 April 2004, which included a proposal from Cooper & Dunham for reinstating the above application.

After consultation with our US partner we have come to the conclusion that the Petition to Withdraw the Holding of Abandonment in this case appears to be in order. Please request that Cooper & Dunham proceed. However, as mentioned on several previous occasions, please note that we that we are still waiting for a detailed explanation from Cooper & Dunham.

Please also be advised that SCI expects to be reimbursed for all expenses and any related costs (including damages) that have been incurred or will be incurred as a result of the abandonment of this application. We would also like to make it very clear that SCI will not pay or reimburse any expenses for the reinstatement of this US application to either Vereenigde or Cooper & Dunham. We kindly ask you to pass this message on to your US partner.

We would appreciate if you would keep us informed on all future developments.

Yours sincerely,
SEED CAPITAL INVESTMENTS (SCI) B.V.

W.J.M. de Vette
Director

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Tel.+31 (0)30 296 5347

Prof. Bronkhorstlaan 26
3723 MB Bilthoven
the Netherlands
Fax.+31 (0)30 294 1526

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ABN-Amro Bank 45.25.35.980 KvK Utrecht 30128806

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer: **0 456 197 A1**

(12) EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: **91107423.5**

(22) Anmeldetag: **07.05.91**

(51) Int. Cl.5: **C07K 7/08**, C07K 7/10, A61K 37/02, A61K 39/42, G01N 33/569

(30) Priorität: **10.05.90 DE 4015044**

(43) Veröffentlichungstag der Anmeldung: **13.11.91 Patentblatt 91/46**

(84) Benannte Vertragsstaaten: **AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

(71) Anmelder: **BEHRINGWERKE Aktiengesellschaft**
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(74) Vertreter: **Becker, Heinrich Karl Engelbert, Dr. et al**
HOECHST AKTIENGESELLSCHAFT Central Patent Department P.O. Box 80 03 20
W-6230 Frankfurt am Main 80(DE)

(54) Seroreaktive Epitope auf Proteinen des menschlichen Papillomavirus (HPV) 18.

(57) Die Erfindung betrifft seroreaktive Epitope auf Proteinen des menschlichen Papillomavirus HPV18.
Außerdem betrifft die Erfindung Peptide, die Aminosäuresequenzen besitzen, die ganz oder teilweise mit den Sequenzen der seroreaktiven Epitope übereinstimmen und Impfstoffe, die solche Peptide enthalten.

EP 0 456 197 A1

Die Erfindung betrifft Seroreaktive Regionen auf den Proteinen E1, E6 und E7 des menschlichen Papillomavirus (HPV) 18.

Weiterhin betrifft die Erfindung Impfstoffe, die Peptide enthalten, welche Aminosäuresequenzen der seroreaktiven Regionen der genannten Virusproteine umfassen und diagnostische Kits, welche die genannten Peptide enthalten.

HPV18 ist ein spezieller Typ des menschlichen Papillomavirus, der das erste Mal in Proc. Natl. Acad. Sci., USA 80, 3813-3815 (1983) beschrieben wurde.

Die DNA-Sequenz und die Organisation des viralen Genoms von HPV18 wurde in Virology 145, 181-185 (1985) publiziert.

HPV18 induziert nicht nur gutartige Schädigungen des Anogenitaltrakts, sondern auch maligne Tumoren des Uterushalses, des Penis und der Scheide. Zudem findet sich HPV18 jedoch in genitalen Ausschabungen von klinisch symptomlosen Individuen. Bis heute ist über die Immunantwort, die auf eine Infektion durch HPV18 und andere Papillomaviren erfolgt, wenig bekannt.

In ersten Experimenten wurden menschliche Seren von STD-Patienten, von Patienten, die an zervikalen Tumoren leiden und von gesunden Individuen auf die Anwesenheit von Antikörpern, die gegen virale Proteine gerichtet sind, getestet. Diese viralen Proteine wurden als Fusionsproteine, die an verschiedene prokaryotische Peptide über ihren N-Terminus kovalent gebunden waren, exprimiert. Solche Fusionsproteine wurden dann als Antigene in Western-Blot-Experimenten verwendet. Dieser Test ist jedoch relativ langwierig und kompliziert und nur mit großem Aufwand durchzuführen, so daß er nicht für eine quantitative Analyse von großen Mengen menschlichen Serums geeignet erscheint. Außerdem ist dieser Test nicht sehr spezifisch, weil die verschiedenen Papillomavirus-Typen auch im Hinblick auf ihr Proteincore verwandt sind und dadurch eine Kreuzreaktion von Antikörpern mit Proteinen bzw. Fusionsproteinen verschiedener Papillomavirus-Typen nicht ausgeschlossen werden kann.

Die Aufgabe der vorliegenden Erfindung ist deshalb die Identifizierung von viralen Strukturen des HPV18, die als Hilfsmittel in der Prophylaxe, der Diagnose und der Therapie von HPV18-induzierten Krankheiten des Menschen geeignet sind. Das Wissen um solche Strukturen (Proteindomänen) ist eine Voraussetzung für die Etablierung eines Tests mit dem große Mengen menschlichen Blutserums auf Anwesenheit von spezifischen HPV geprüft werden können.

Die vorliegende Erfindung umfaßt insofern ein serorekatives Epitop auf dem E1-Protein von HPV18 mit der folgenden Aminosäuresequenz

TENSPLGERLEVDTELSPRLQEISLNS

sowie seroreaktive Epitope auf dem E6-Protein von HPV18 mit einer der folgenden Aminosäuresequenzen

I. DPTRRPYKLPDLCTELNTSLQDIEITCVYCKT

II. MARFEDPTRRPYKL

III. AACHKCIDFYSRIRELRHYSDSVYGDTLEKLT

sowie seroreaktive Epitope auf dem E7-Protein von HPV18 mit einer der folgenden Aminosäuresequenzen

I. VLHLEPQNEIPVDLLCHEQLSDSEEENDEIDGVNHQHLPARRAEPQRH und

II. IDGVNHQHLPARR.

Weiterhin umfaßt die Erfindung Peptide, die entweder eine oder mehrere erfindungsgemäße Aminosäuresequenz(en) der oben genannten seroreaktiven Epitope enthalten.

Die Erfindung umfaßt auch Impfstoffe, die auf Peptiden basierten, die eine oder mehrere Aminosäuresequenz(en) der oben genannten seroreaktiven Epitope der Proteine von HPV18 enthalten.

Spezifische Antikörper gegen HPV18 E1-, E6- und E7-Proteine können mit Hilfe eines erfindungsgemäßen diagnostischen Kits in Patientenseren nachgewiesen werden. Dieser Kit enthält die erfindungsgemäßen Peptide.

Im Sinne einer Prophylaxe können auch die spezifischen viralen Proteine, die die seroreaktiven

Regionen enthalten, auch frühzeitig durch polyklonale Antikörper bzw. monoklonale Antikörper, die gegen diese Regionen gerichtet sind, im Blutserum identifiziert werden. Dementsprechend umfaßt diese Erfindung auch einen diagnostischen Kit, der polyklonale oder monoklonale Antikörper enthält, die spezifisch gegen die seroreaktiven Regionen des HPV18 gerichtet sind.

Zur Identifizierung der seroreaktiven Epitope wurden folgende voneinander unabhängige Methoden verwendet:

A. Ein Screening einer "Shot Gun"-Expressionsbank: Die im Bakterienplasmidvektor pSP65 klonierte HPV18-DNA wurde mit Ultraschallscherung und anschließender DNase-Behandlung auf eine durchschnittliche Fragmentgröße von 100 Basenpaaren gebracht. Die Enden dieser Fragmente wurden mit T4 DNA-Polymerase aufgefüllt und in den Phagenexpressionsvektor fuse 1 einligiert. Fuse 1 ist von dem Bakteriophagen fd abgeleitet und in Science 228, 1315-1317 (1985) beschrieben. Die Phagen wurden mit Escherichia coli K91 ausplattiert, Replika auf Nitrocellulosefilter abgezogen und die Filter mit geeigneten polyklonalen Kaninchenseren inkubiert. Positive Klone wurden in mehreren Vereinzelungsschritten isoliert und die immunreaktiven Peptidsequenzen durch DNA-Sequenzierung identifiziert.

B. Peptidüberlappung
127 überlappende Peptide, die kurzen Stücken der HPV18E6- und -E7-Proteine entsprechen, wurden an Polyethylen-"pins" synthetisiert, wobei die Fmoc-Chemie verwendet wurde (Proc. Natl. Acad. Sci., 82, 178 (1985)). Die Proteinsequenz der E6- und E7-Proteine wurde in 10mere unterteilt, die in 8 Aminosäuren mit dem nächsten Peptid übereinstimmen. Die Peptide wurden in den entsprechenden Antiseren durch ELISA ausgetestet.

Beispiel 1

Derivate des filamentösen Phasgen fd wurden benutzt um ein Expressionssystem für HPV18 DNA-Fragmente zu erhalten. Dazu wurde fuse 1 (fd-tet-J6, Science 228, 1315-1317 (1985); Gene 73, 305-318 (1988)) an der einzigen PvuII-Schnittstelle geschnitten. Genomische HPV18 DNA-Fragmente aus einem DNaseI-Verdau nach DNA-Repair wurden mit einer T4-DNA-Ligase blunt-end einligiert. Zur Transformation des fuse 1-Vektors wurde der E. coli Stamm K802 (FgalK2 galT22 metB1 supE44 hsdr(2); Journal of Molecular Biology 16, 118-133 (1966)) nach dem Verfahren von Hanahan aus Journal of Molecular Biology 166, 557-580 (1988) verwendet. Die tet-resistenten Kolonien produzieren Bacteriophagen, die für die Bakterien wegen ihres F-Phänotyps nicht infektiös sind. Um die Phagen auszuplattieren wurde der E. coli Stamm K91 (F^+, ein Derivat von E. coli K38, Virology 49, 45-60 (1972)) verwendet.

Beispiel 2

Ungefähr 50 000 rekombinierte Phagen aus der oben beschriebenen Random-Bank wurden mit 0,2 ml exponentiell wachsenden E. coli K91-Zellen in 3,5 ml 0,5 % Agarose, die 10 mM $MgSO_4$ enthielt, auf Minimalagarplatten ausplattiert. Replika der Platten wurden auf Nitrocellulosefilter abgezogen und dann 6 h lang bei 37 °C weiter auf frischem Minimalagar inkubiert, um das Signal zu verstärken. Danach wurden die Filter 60 min lang mit 10 % fettarmer Milch in PBS geblockt und über Nacht in 5 % Milch-PBS mit einer Verdünnung von HPV-spezifischen Antisera von 1:100 bis 1:1000 inkubiert. Statt der spezifischen HPV-Antisera können auch monoklonale Antikörper verwendet werden. Die Antisera wurden mit beschallten K91-Zellen präadsorbiert. Die Filter wurden dann 5x gewaschen und zwar 5 min lang in einer PBS/0,1 % Tween 20 und dann 3 h lang bei Raumtemperatur mit Ziegen-anti-Kaninchen-Antikörper oder, im Fall der Verwendung monoklonaler Antikörper, anti-Maus-Peroxidase-Antikörper (1:1000) in 5% fettarmer Milch inkubiert. Nach Waschen der Filter wurden sie in 50 ml PBS, das 30 mg Diaminobenzidin, 30 µl %iges H_2O_2 und 1,5 ml 1 %iges $NiSO_4$ enthielt, gefärbt. Danach wurden die Filter 30 min lang in H_2O gewaschen und danach auf Filterpapier getrocknet.

Mit dem polyklonalen Kaninchenserum gegen HPV18 E7 wurden primär 25 Phagen isoliert, von denen sich 18 in den weiteren Aufreinigungsschritten als positiv erwiesen. Anschließend wurden Phagenpartikel in Kultur angezüchtet und Einzelstrang-DNA präpariert.

Beispiel 3

Derselbe Ansatz wie in Beispiel 2 wurde auch für HPV18 E6-Protein gewählt. Da das verwendete polyklonale Kaninchenserum Kreuzreaktionen mit nichtviralen Epitopen aufwies, wurde neben der Western-Blot-methode mit spezifischen DNA-Fragmenten geprobt, um unter allen reaktiven Rekombinanten solche mit HPV18 E6-Anteilen zu identifizieren. Aus 70 000 rekombinanten Phagen wurden 15 isoliert und

schließlich sequenziert. Das Epitop HPV18 E6 Nr. 1 wurde so zum Beispiel in der untersuchten Phagenbank insgesamt 10 mal gefunden.

Beispiel 4

Präparation von Einzelstrang-DNA aus fuse 1-Rekombinanten

Hierzu wurde eine Vorschrift aus Proc. Natl. Acad. Sci., USA 74, 5463-5467 (1977) verwendet. 50 ml LM wurden mit tet-resistenten E. coli K91-Zellen inkubiert, die das fuse 1-Plasmid trugen und dieser Ansatz wurde 16 h lang bei 37 °C inkubiert. Die Bakterien wurden dann bei 6000 rpm 30 min lang pelletiert. Nach dem Hinzufügen von 2 ml 40 %igem PEG 6000 und 2 mml 5 M Natriumacetat, pH 6,5 zum Überstand wurden die Phagen bei 0 °C 60 min lang präzipitiert und das Präzipitat bei 6000 rpm 60 min lang zentrifugiert. Das Pellet wurde in 0,3 ml TE resuspendiert. Nach zwei Extraktionen mit Phenol wurde die DNA präzipitiert. Ungefähr 25 % der Präparationen wurden dann zur Sequenzierung verwendet.

Beispiel 5

Sequenzierung

Zur DNA-Sequenzierung wurde die Standard-USB (United States Biochemicals)-Methode (USB, 1987) verwendet. Der universale Primer wurde durch ein 20mer Oligonucleotid (5'-TCCAGACGTTAGTAAATGAA-3') ersetzt.

Beispiel 6

Peptid-Synthese

127 überlappende Peptide, die in kurzen Stücken die ORFs HPV18 E6 und -E7 darstellen, wurden nach der Fmoc-Chemie an Polyethylen-"pins" synthetisiert, wie in Proc. Natl. Acad. Sci. 32, 178 (1985) und Proc. Natl. Acad. Sci. 81, 3998 (1985) beschrieben. Die Polyethylen-"pins", die mit β-Alanin derivatisiert wurden, wurden von CRB England erhalten. Abweichend von oben zitierten Publikationen wurde die Proteinsequenz in Dekapeptide eingeteilt, die mit dem Nachbarpeptid um 8 Aminosäuren überlappen. Die Synthese wurde ausgeführt mit Hilfe der Fmoc-Chemie und in situ-Aktivierung durch BOP (Castro's Reagens) (Tetrahedron Letters, 14, 1219 (1975)). Fmoc-Aminosäurederivate (6 µmol), BOP und N-Methylmorpholin-Lösung wurden in Polyethyleneinsätze (CRB) entsprechend der Peptidsequenz, die synthetisiert werden soll, verteilt. Alle anderen Reaktionen wurden nach dem CRB-Protokoll ausgeführt.

Beispiel 7

Die Polyethylen-"pins" wurden nach dem ELISA-Testverfahren mit den oben genannten polyklonalen Kaninchenseren inkubiert, gebundene Antikörper mit Protein-A-Peroxidase nachgewiesen. Ein durch unspezifische Bindungen entstehender Background wurde durch Protein-A-Inkubation ohne ersten Antikörper quantifiziert. Die reaktiven Peptide liegen in Bereichen, die durch das Phagenscreening als seroreaktives Epitop identifiziert wurden.

Alle Tests wurden an den Peptiden, die kovalent an die Polyethylen-"pins" gebunden vorliegen und an die sie ursprünglich auch synthetisiert wurden, durchgeführt. Racks mit 96 pins, die in einer solchen Konfiguration fixiert waren, daß sie in die Löcher von Miktrotiter-Platten eingebracht werden konnten, wurden benutzt. Die Inkubation für den ELISA wurde durchgeführt, während die pins in die Löcher hineingetaucht wurden. Die pins wurden mit Methanol und PBS gewaschen und danach mit 0,25 % Gelatine, 0,1 % Tween 20 in PBS 2 h lang bei 37 °C geblockt, gefolgt von einer 1 h Inkubation bei 37 °C mit Seren, die 1:200 bis 1:4000 in 0,125 % Gelatine und 0,05 % Tween 20 verdünnt wurden. Nach einem weiteren Waschschritt mit PBS/0,1 % Tween 20 wurden die pins 1 h lang bei 37 °C mit Protein-A-Peroxidase 1:4000 inkubiert, gefolgt von einem weiteren Waschschritt und Färben mit Tetramethylbenzidin (TMB) 15 min lang. Der Färbeschritt wurde durch Herausziehen der pins aus der Färbelösung und Hinzufügen von 100 µl einer 0,2 molaren H_2SO_4-Lösung beendet. Die Absorption wurde dann an einem automatischen ELISA-Reader gemessen. Um den Antikörper-Enzym-Komplex nach dem ELISA-Verfahren zu entfernen, wurden die pins für 1 h mit Ultraschall (Wasserbad, 30 W, 48 kHz) bei 60 °C in PBS/1 % SDS/0,1 % β-Mercaptoethanol inkubiert und wurden schließlich mit Methanol gewaschen. Die Effektivität

dieser Prozedur wurde mit Hilfe von ELISA unter Verwendung von Protein A/Peroxidase ohne Beteiligung eines primären Serums ausgetestet. Die gleichen Peptide wurden mehr als 40 mal in den folgenden ELISA's getestet.

Tabelle

Seroreaktives Epitop E1 (HPV18)

bpl1193-TENSPLGERLEVDTELSPRLQEISLNS-bp1273

Seroreaktives Epitop E6 (HPV18)

pb120-DPTRRPYKLPDLCTELNTSLQDIEITCVYCKT-bp215

MARFEDPTRRPYKL

bp294-AACHKCIDFYSRIRELRHYSDSVYGDTLEKLT-bp386

Seroreaktives Epitop E7 (HPV18)

bp623-VLHLEPQNEIPVDLLCHEQLSDSEEENDEIDGVNHQHLPARRAEPQRH-bp763

IDGVNHQHLPARR

Patentansprüche

1. Seroreaktives Epitop auf dem E1-Protein von HPV18 mit der folgenden Aminosäuresequenz

TENSPLGERLEVDTELSPRLQEISLNS

2. Seroreaktive Epitope auf dem E6-Protein von HPV18 mit einer der folgenden Aminosäuresequenzen

I. DPTRRPYKLPDLCTELNTSLQDIEITCVYCKT

II. MARFEDPTRRPYKL

III. AACHKCIDFYSRIRELRHYSDSVYGDTLEKLT

3. Seroreaktive Epitope auf dem E7-Protein von HPV18 mit einer der folgenden Aminosäuresequenzen

I. VLHLEPQNEIPVDLLCHEQLSDSEEENDEIDGVNHQHLPARRAEPQRH

II. IDGVNHQHLPARR.

4. Peptide, dadurch gekennzeichnet, daß sie eines oder mehrere der seroreaktiven Epitope nach den Ansprüchen 1 bis 3 enthalten.

5. Vakzine, dadurch gekennzeichnet, daß sie eines oder mehrere der Peptide nach Anspruch 4 enthalten.

6. Diagnostische Zubereitung für die Identifizierung von spezifischen Antikörpern, die gegen die Proteine E1, E6 oder E7 von HPV18 gerichtet sind, dadurch gekennzeichnet, daß sie eines oder mehrere der Peptide nach Anspruch 4 enthält.

7. Diagnostische Zubereitung für die Identifizierung von viralen Proteinen in Patientenseren, dadurch gekennzeichnet, daß sie polyklonale oder monoklonale Antikörper mit Spezifität für die Epitope nach Ansprüchen 1 bis 3 und/oder Spezifität für Peptide nach Anspruch 4 enthält.

Patentansprüche für folgenden Vertragsstaat: ES

1. Verfahren zur Herstellung von Impfstoff gegen HPV, dadurch gekennzeichnet, daß eines oder mehrere der Peptide von HPV 18 mit der Aminosäuresequenz

TENSPLGERLEVDTELSPRLQEISLNS

des E1-Proteins

oder mit den Aminosäuresequenzen

I. DPTRRPYKLPDLCTELNTSLQDIEITCVYCKT
II. MARFEDPTRRPYKL
III. AACHKCIDFYSRIRELRHYSDSVYGDTLEKLT

des E6-Proteins

oder mit den Aminosäuresequenzen

I. VLHLEPQNEIPVDLLCHEQLSDSEEENDEIDGVNHQHLPARRAEPQRH
II. IDGVNHQHLPARR

des E7-Proteins

mit üblichen Adjuvantien und Hilfsstoffen gemischt und für Impfdosen konfektioniert werden.

2. Verfahren zur Herstellung eines Diagnostikums, dadurch gekennzeichnet, daß eines oder mehrere der Peptide von HPV 18 mit der Aminosäuresequenz

TENSPLGERLEVDTELSPRLQEISLNS

des E1-Proteins

oder mit den Aminosäuresequenzen

I. DPTRRPYKLPDLCTELNTSLQDIEITCVYCKT
II. MARFEDPTRRPYKL
III. AACHKCIDFYSRIRELRHYSDSVYGDTLEKLT

des E6-Proteins

oder mit den Aminosäuresequenzen

I. VLHLEPQNEIPVDLLCHEQLSDSEEENDEIDGVNHQHLPARRAEPQRH
II. IDGVNHQHLPARR

des E7-Proteins

an der Oberfläche eines geeigneten Trägermaterials fixiert wird.

3. Verfahren zur Herstellung eines Diagnostikums, dadurch gekennzeichnet, daß poly- oder monoklonale Antikörper gegen eines oder mehrere der Peptide von HPV 18 mit der Aminosäuresequenz

TENSPLGERLEVDTELSPRLQEISLNS

des E1-Proteins

oder mit den Aminosäuresequenzen

I. DPTRRPYKLPDLCTELNTSLQDIEITCVYCKT
II. MARFEDPTRRPYKL
III. AACHKCIDFYSRIRELRHYSDSVYGDTLEKLT

des E6-Proteins

oder mit den Aminosäuresequenzen

I. VLHLEPQNEIPVDLLCHEQLSDSEEENDEIDGVNHQHLPARRAEPQRH
II. IDGVNHQHLPARR

des E7-Proteins

eingesetzt werden.

Europäisches Patentamt

EUROPÄISCHER RECHERCHENBERICHT

Nummer der Anmeldung

EP 91 10 7423

EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.5)
A	EP-A-0 257 754 (STANFORD UNIVERSITY) * Das ganze Dokument, insbesondere Seite 2, Zeilen 10-25; Seite 3; Seite 5, Zeile 25 - Seite 6, Zeile 26 *	1-5	C 07 K 7/08 C 07 K 7/10 A 61 K 37/02 A 61 K 39/42
A	CHEMICAL ABSTRACTS, Band 107, Nr. 7, 17. August 1987, Seite 191, Zusammenfassung Nr. 53075n, Columbus, Ohio, US; S.T. COLE et al.: "Nucleotide sequence and comparative analysis of the human papillomavirus type 18 genome. Phylogeny of papillomaviruses and repeated structure of the E6 and E7 gene products", & J. MOL. BIOL. 1987, 193(4), 599-608 * Zusammenfassung *	1-5	G 01 N 33/569
A	CHEMICAL ABSTRACTS, Band 106, Nr. 1, 5. Januar 1987, Seite 112, Zusammenfassung Nr. 1115k, Columbus, Ohio, US; G. MATLASHEWSKI et al.: "The expression of human papillomavirus type 18 E6 protein in bacteria and the production of anti-E6 antibodies", & J. GEN. VIROL. 1986, 67(9), 1909-16 * Zusammenfassung *	1-5	

RECHERCHIERTE SACHGEBIETE (Int. Cl.5)
C 07 K A 61 K G 01 N

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt

Recherchenort	Abschlußdatum der Recherche	Prüfer
Den Haag	18 August 91	MASTURZO P.

KATEGORIE DER GENANNTEN DOKUMENTE

X: von besonderer Bedeutung allein betrachtet
Y: von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A: technologischer Hintergrund
O: nichtschriftliche Offenbarung
P: Zwischenliteratur
T: der Erfindung zugrunde liegende Theorien oder Grundsätze

E: älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D: in der Anmeldung angeführtes Dokument
L: aus anderen Gründen angeführtes Dokument

&: Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

Dkt. 45113/RDK

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

Applicants	:	KAST, Wybe Martin et al.
U.S. Serial No.	:	08/170,344
U.S. Filing Date	:	March 30, 1994
For	:	PEPTIDES OF HUMAN PAPILLOMA VIRUS FOR USE IN HUMAN T CELL RESPONSE INDUCING COMPOSITIONS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MARK EINERHAND

Sir:

I, Mark Einerhand, hereby declare as follows:

1. I am a registered European Patent Attorney, and a member of the firm of Vereenigde, headquartered in The Hague, The Netherlands. I am a European Patent attorney for the University of Leiden, the assignee of the above-identified application. I am the European Patent attorney responsible for the prosecution of the above-identified application at Vereenigde.

2. In 1994, my firm engaged Cooper & Dunham LLP to file a U.S. patent application for this invention. Mr. Thomas Moran, one of our U.S. correspondents, filed this application on March 30, 1994 and reported its filing to our firm.

3. I am informed that the application underwent examination, and that Office Actions were mailed on October 4, 1994 and August 23, 1995 to which Mr. Moran filed a response on April 4, 1995 and February 23, 1996 respectively.

4. I am further informed that Cooper & Dunham moved its offices from 30 Rockefeller Plaza, New York, New York to 1185 Avenue of the Americas, New York, New

York in late 1994. While we became aware of the change of address sometime in 1994 or 1995, we were unaware that Mr. Moran apparently did not file a change of address notification form for this application. Our foreign correspondents generally would not send us a copy of such a document.

5. I have reviewed our file for this matter, and can state that our firm was unaware that an Office Action was issued in this case on June, 1996, nor were we aware that the United States Patent & Trademark Office issued either an Office Action on June 14, 1996 or a Notice of Abandonment on January 13, 1997. Our file contains no correspondence from Cooper & Dunham during that time period. As mentioned in Mr. Katz's declaration, our firm contacted Cooper & Dunham on December 10, 1997 to ask for a copy of the claims as amended (see Katz Declaration, Ex. 5). We were unaware that a Notice of Abandonment had been mailed by the U.S. Patent and Trademark Office.

6. We first became aware of the possible abandonment when our Records Department on January 20, 2004, sent a status inquiry to Cooper & Dunham to ask about the status of the U.S. application (Ex. A hereto). I am informed that when Cooper & Dunham received our status inquiry, they checked the status of the application on the PTO website, and informed us on February 5, 2004 that the application had gone abandoned in January, 1997 (Ex. B).

7. We sent Mr. Katz of Cooper & Dunham a fax on February 27, 2004 requesting information regarding a possible revival of the application (Exhibit C). In response, Mr. Katz faxed us on February 27, 2004 that he had ordered the file from the USPTO, but that they had thus far not received it (Exhibit D). On around March 8, 2004, we informed the client/investor that the application had become abandoned and that we were investigating the

possibility of reviving the application. On March 17, 2004, we received from Cooper & Dunham a copy of the last Office Action that was issued in this case (Exhibit E). This was reported by us to the client/investor on March 23, 2004 (Exhibit F). On March 30, 2004, we received an email from Cooper & Dunham reminding us that they were awaiting instructions on how to proceed. On around April 5, 2004 we received information from one of the inventors for responding to the Office Action. We sent instructions for responding to the Office Action and an amended set of claims to Cooper & Dunham on April 8, 2004 (Exhibits G and H). On April 21st and 28th, Cooper & Dunham mailed us a draft petition to revive the application, a draft response to the Office Action, a draft request for removal of the finality of the Office Action and a draft terminal disclaimer. These were forwarded to the client/investor on April 29, 2004 (Exhibits I-M). On May 18, 2004, our client informed us that they consulted their licensee and agreed with the proposal for the petition to revive the application and instructed us to inform Cooper & Dunham that they could proceed with the filing of the petition to revive the application (Exhibit N). Since the terminal disclaimer required the signature of the assignee, we contacted Mr. Katz to discuss the filing of the petition to revive the application. After further consultation with the client/investor, we decided not to wait for the signature of the Rijksuniversiteit Leiden, (University of Leiden) but instead to file the petition with an unsigned terminal disclaimer, and a representation that the terminal disclaimer would be filed as soon as received. A written confirmation of this instruction was sent by facsimile on June 1, 2004 (Exhibit O). We received the signed terminal disclaimer on June 30, 2004 (Exhibit P) and forwarded it to Cooper & Dunham on July 1, 2004 (Exhibit Q).

8. On information and belief, and after inquiry, I can state that the personnel at Vereenigde as well as the inventors themselves and the personnel at the assignee University

of Leiden were unaware that the application had become abandoned from January 1997 until February 2004. The delay in filing a response to the June, 1996 Office Action was entirely unintentional, and was due to lack of receipt of the June, 1996 Office Action from Cooper & Dunham LLP. Thus, the delay in filing a response to the June, 1996 Office Action from January 13, 1997 until the filing of a grantable petition was entirely unintentional on the part of my firm, the inventors, the assignee and the investor. Neither the inventors, nor the assignee, nor the investor had any intention or desire to abandon the application. On the contrary, counterparts of the application have been prosecuted in other countries, and the application has been licensed world-wide to an entity that is seeking to commercialize the invention disclosed and claimed in the application. I attach as Exhibit 1 a list showing that applicants have been pursuing the foreign counterparts of this application to issuance throughout the world.

9. The Vereenigde firm, the assignee and the investor acted with reasonable diligence in pursuing revival of the application. After inquiring about the status of the application in January 2004, and learning that the application had become abandoned, we asked Cooper & Dunham LLP to try to determine how the application had gone abandoned, and to see if it could be revived.

10. When we received the copy of the June, 1996 Office Action from Cooper & Dunham LLP, we notified our client, and advised them of the petition to revive procedure, and of the need to file a terminal disclaimer. On information and belief, the assignee/investor had to contact the licensee to inform them of the problem and confirm that they sought to revive the application. Further, the office action was received, and instructions were prepared to enable our U.S. counsel to respond to the June, 1996 Office Action. As soon as they

authorized us to proceed, we notified Cooper & Dunham to file a petition to revive. Cooper & Dunham promptly filed the petition upon receipt of our instructions to do so.

11. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: August 18, 2004

Mark Einerhand

Den Haag • Groningen • Arnhem • 's-Hertogenbosch • Amersfoort • Nijmegen

Patent Attorneys
Trademark Attorneys
Attorneys-at-Law

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Cooper & Dunham
1185 Avenue of the Americas
New York, N.Y. 10036
USA

Your ref. 45113
Our ref. ME/P20884US00

Den Haag,
January 20, 2004

Re.: Patent Application in the U.S. of America No. 08/170,344
for
of RIJKSUNIVERSITEIT LEIDEN

Could you please supply us with a status report of the above mentioned application as we have not heard from you since January 28,1998.

Yours faithfully,
VEREENIGDE

Records Department
A. Rozendaal

V313.1

Exhibit A

P2088W300

COOPER & DUNHAM LLP
1185 Avenue of the Americas, New York, New York 10036

FACSIMILE TRANSMISSION
Telephone No.: 212-278-0400 / Facsimile No.: 212-391-0526

ONTVANGEN
06 FEB 2004
AMERSFOORT

PLEASE DELIVER THE FOLLOWING PAGES

TO	:	Dr. J. Renes
COMPANY	:	Vereenigde Octrooibureaux
FAX NO.	:	011-31-70-416-6799
FROM	:	Robert D. Katz, Esq.

TOTAL NUMBER OF PAGES, INCLUDING COVER PAGE: 3

DATE : February 5, 2004

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Exhibit B

COOPER & DUNHAM LLP

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ANNE C. MARINOVIC, PH.D.
ANTHONY C. KHONG, PH.D.
JOHN R. RABERMAN, PH.D.

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www.cooperdunham.com

*NEW YORK STATE BAR ADMISSION PENDING

WRITER'S DIRECT DIAL: 212.278.0424
WRITER'S EMAIL: rens@cooperdunham.com

February 5, 2004

VIA FACSIMILE

Dr. J. Renes
VEREENIGDE
P.O. Box 87930
2508 DH The Hague
Netherlands

Re: Your prev. ref. Ren/92028-310 - Wybe Martin Kast et al.
Peptides of Human Papilloma Virus for Use in
Human T Cell Response Inducing Compositions
Serial No. 08/170,344 filed March 30, 1994
Your ref. No. ME/P20884US00; Our Docket 45113

Dear Dr. Renes:

In response to your inquiry of January 20, 2004, I have reviewed the file. We are investigating the matter in the Patent Office. I suspect that Mr. Moran never informed the Patent Office that we moved offices, and we never received any correspondence from the Patent Office after our forwarding service expired.

If this turns out to be true, we should be able to revive the application, but will have to file a terminal disclaimer to do so. We will have to disclaim the time period in which the application was unintentionally abandoned.

I will let you know as soon as I learn anything further. I apologize on behalf of the firm for this error.

Very truly yours,

Bob Katz

Robert D. Katz

RDK/sd

Den Haag • Groningen • Arnhem • 's-Hertogenbosch • Amersfoort • Nijmegen

Patent Attorneys
Trademark Attorneys
Attorneys-at-Law

VEREENIGDE

BY FACSIMILE: +1 212 391 0525
Cooper & Dunham
1185 Avenue of the Americas
New York, N.Y. 10036
USA

Nieuwe Parklaan 97

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The Netherlands

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e-mail patent@vereenigde.nl
trademark@vereenigde.nl
legal@vereenigde.nl

www.vereenigde.com

Your ref. 45113
Our ref. ME/P20884US00

Den Haag,
February 27, 2004

Re: Patent Application in the U.S. of America No. 170344
in the name of RIJKSUNIVERSITEIT LEIDEN

Dear Mr. Katz,

Thank you for your letter of February 5, 2004 in the above-identified patent application.

Could you please inform me whether you have already received word regarding the revival of this application.

Very truly yours,
VEREENIGDE

M. Einerhand

ne

Exhibit C

V. III

COOPER & DUNHAM LLP

ATTORNEYS AT LAW

1185 AVENUE OF THE AMERICAS, NEW YORK, NEW YORK 10036

TELEPHONE: (212) 278-0400

aflag

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(212) 391-0690

February 27, 2004

*NEW YORK STATE BAR ADMISSION PENDING

WRITER'S DIRECT DIAL: 212.278.0424
WRITER'S EMAIL: rkatz@cooperdunham.com

VIA FACSIMILE

VEREENIGDE
P.O. Box 87930
2508 DH The Hague
Netherlands

Attn: Mark Einerhand

Re: Your prev. ref. Ren/92026-310 - Wybe Martin Kast et al.
Peptides of Human Papilloma Virus for Use in
Human T Cell Response Inducing Compositions
Serial No. 08/170,344 filed March 30, 1994
Your ref. No. ME/P20884US00; Our Docket 45113

Dear Mr. Einerhand:

We have ordered the file in the USPTO, but thus far it has not been located. We have contacted the examiner and she no longer has the file. We will discuss the matter with the examiner. We can reconstruct the file and continue with prosecution from that point.

Once again, on behalf of the firm, we apologize for this error.

Sincerely,

Robert D. Katz

RDK/sd

LOCATION:+2123910525 RX TIME 27.02.'04 22:39

Exhibit D

Veveiros file

Facsimile Transmision

TO: Robert Katz Ref: 08[redacted]

FAX: 212 3910525 DATE 3-17-04 pages incl. cover 3

From: Helene Stanonik

PLAZA MAILBOXES
2101 CRYSTAL PLAZA ARCADE
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COOPER & DUNHAM LLP
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ROBERT D. KATZ

Exhibit E

LOCATION:+2123910525 RX TIME 17.03.'04 21:18

Serial Number: 08/170344

Art Unit: 1802

Part III. DETAILED ACTION

Response to Amendment

15. Applicants' amendment filed February 26, 1996 is acknowledged and has been entered. Claims 1, 19-22, and 24 have been cancelled. Claims 2-8 and 10-18 have been amended. New claim 25 has been added. Claims 2, 4-18, and 25 are now pending in the present application. All prior rejections are withdrawn with the exception of those discussed below.

16. The text of the 35 U.S.C. Code not included in this Office Action can be found in the prior Office Action.

17. The information disclosure statement filed January 4, 1994 fails to comply with 37 CFR § 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in § 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicants state (April 17, 1995) that a substitute IDS will be filed, however it has not been received.

The present amendment filed (2-26-96) directed the Examiner to the April 7, 1995 amendment with respect to the content and relevance of the publications refered to in the IDS. The IDS references that have not been considered are EP0375555 and EP0456197. Applicants have not provided an english translation nor a statement of content and relevance of these references in any of the amendments. These references have not been considered as to the merits.

18. The objection to the specification and rejection of claims 2, 4-18 (and now claim 25) under 35 U.S.C. § 112, first paragraph (i.e. lack of an enabling disclosure) is maintained.

This rejection is maintained for essentially the same reasons as the rejection of claims 1-22 and 24 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. The disclosure is enabled for nonapeptide sequences from the E6 or E7 genes of HPV16 or HPV18, and MHC Class I molecules as specifically taught in the specification. The specification has not provided sufficient evidence of a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. Matlashewski et al. discloses that HPV18 proteins (E6 gene) maybe diagnostically useful since the proteins have been identified in specific human cancers, however the methods as claimed in this invention are not known in the art. Accordingly, amendment of the claims to what is supported in the specification or filing of evidence in the form of a Rule 132 declaration providing factual evidence supporting the broad range claims is suggested.

A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which it pertains to make and use the invention as of its filing date, In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques where necessary, as to enable those persons skilled in the art to make and utilize the invention.

Specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. Where the constitution and formula of a compound is stated only as probability and speculation, the disclosure is not sufficient to support claims identifying the compound by

such composition or formula. A disclosure involving a new chemical compound or composition must teach persons skilled in the art how to make the compound. Incomplete teachings may not be completed by reference to subsequently filed applications.

The instant specification invites the skilled artisan to experiment. The factor which must be considered in determining undue experimentation are set forth in Ex parte Forman 230 USPQ 546. The factors include 1) quantity of experimentation necessary, 2) the amount of guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the predictability of the art and the 7) breath of the claims. With regard to factors three and six, it is noted that there are no working examples or support for in vivo efficacy of the active ingredients in a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition, or peptides from any HPV that bind to MHC Class I molecules. Such is not seen as sufficient to support the breath of the claims, wherein the scope of the claims encompasses how to prepare a peptide from any of the listed HPV proteins (or any other HPV protein) wherein the peptide binds to any human MHC Class I molecule. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves., see In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Applicants have argued that the specification is enabled and have cited Ruppert et al., Kast et al., Feltkamp et al., Vitiello et al., and Ressing et al. as support to demonstrate enablement, however it is noted that the specification must be enabled as of its filing date. Prior art references that were published after Applicants' effective filing date (5-5-92) cannot be used to rebut prima facie case of nonenablement under 35 USC 112. In re Glass, 181 USPQ 31; 492 F2.d 1228 (CCPA 1974).

Applicants have argued that it would be unethical to demonstrate HPV treatment in humans, however the Examiner has not suggested such a demonstration. Applicants have not demonstrated treatment of HPV in animal models. With regard to the method of

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prophylactic or therapeutic treatment, it appears that the specification is a paper protocol. The specification does not show any therapy or prophylactic treatment, only in vitro studies; no animal studies using the peptides to demonstrate prophylactic or therapy treatment that would correlate to human efficacy have been set forth in the specification.

Applicants have argued that Kast et al. (1991, PNAS 88:2283-2287 and 1991, Immunol. Letters 30(2):229-232) show that one of skill in the art would readily understand from these references how to make and use the claimed invention. Kast et al. (1991, PNAS) disclose the immunization of synthetic peptides of Sendai virus, not HPV. Further, Kast et al. (1991, Immunol. Letters) does disclose the use of peptide vaccination, however the use of HPV peptides is not discussed. HPV is discussed with regard to using "... cultured human CTL for immunotherapy of virus-induced tumors" (p. 229). Furthermore, the reference discloses that there are several unanswered questions regarding peptide vaccination as a novel immunotherapeutic or preventive approach in man (summary; p. 230, col. 2).

In response to Applicant's argument that Matlashewski et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides that bind in the groove on top of an MHC Class I molecule) are not stated in the claims. Therefore, it is irrelevant whether the reference includes these features or not.

Applicant's arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Applicants have asserted that as the methods claims directed to methods of prophylactic or therapy treatment of a human have been cancelled that this objection should be eliminated. However, claims (16-18) directed a pharmaceutical composition containing a prophylactically or therapeutically effective amount for eliciting cellular immune response of a peptide and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant are not enabled for the same reasons as methods claims. The claims as presently written indicate or suggest that the 'pharmaceutical composition' would be administered to an animal or human,

however the specification is not enabled for such administration as previously indicated. Further, such short peptides require immunogenic carriers to ensure an immune response.

The claims also recite fragments, homologs, isoforms, derivatives genetic variants or conservative variants of the amino acid sequences and that these fragments, homologs, isoforms, derivatives genetic variants or conservative variants of the amino acid sequences will bind to the grooves on top of the MHC Class I molecule. The specification discloses that variants and derivatives include any amino acid substitution, deletion, or other processes (p. 17). Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex (Bowie et al. 1990; p. 1306; p. 1308) and is well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in protein and the result of such modifications is unpredictable based on the instant disclosure.

The specification does not support the broad scope of the claims which encompass all variants of the protein because the specification does not disclose the following: the general tolerance to modification (substitution, insertion, deletion) and extent of such tolerance; specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; what variants, if any, can be made which retain the biological activity of the intact protein; and the specification provide essentially no guidance as to which

of the essentially infinite possible choices is likely to be successful. Further, Houghten et al. teach that changes/modifications (addition, substitution, deletion or inversion) of one or more amino acids in a polypeptide will alter antigenic determinants and therefore effect antibody production (p. 21) as well as antibody binding. Houghten et al. also teach that "... combined effects of multiple changes in an antigenic determinant could result in a loss of [immunological] protection.". and "A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies..." (p. 24). Houghten et al. teach that point mutations at one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen (p. 24). It is not always possible to make the derivatives that retain immunodominant regions and immunological activity if the regions have been altered.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of insertions, deletions or substitutions encompassing a variant, fragment, derivatives, homologs, isoforms etc as presently claimed. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the protein structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins. However, even if it were shown that some modifications could be tolerated in the claimed peptides, for the reasons discussed the claims would still expectedly encompass a significant number of inoperative species which could not be distinguished without undue experimentation. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986).

19. Claims 12 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

This rejection is maintained. It is noted that Applicants attempted to amend these claims with regard to the Markush language, however the instruction for the amendment of these claims is unclear. The line numbers stated in the amendment filed February 26, 1996 are not the same as those in the amendment filed July 18, 1994.

20. The rejection of claims 2, 4, 7, 8, 11, 13, and 15-18 (and now 25) under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103 as obvious over Schoolnik et al. is maintained. This rejection is maintained for essentially the same reasons as the rejection of claims 1, 2, 4, 7, 8, 11, 13, and 15-22 under this statutory provision, as set forth in the last Office action. Applicants' arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Schoolnik et al. discloses synthetic peptides from HPV that are useful in the diagnosis and therapy of conditions associated with HPV infection (abstract; p. 9, l. 10-18; claims). Schoolnik et al. teaches the preparation of peptides from HPV16 (E6 and E7) or other HPV proteins useful to raise antibodies for diagnostic, protective (i.e. prophylactic), and therapeutic purposes and vaccines, as well as various mode of administration (p. 3, l. 1-39; p. 5, l. 28-50; p. 4, l. 27 to p. 5, l. 24; p. 7, l. 47 to p. 8, l. 8).

It is noted that the claims recite a peptide comprising an amino acid sequence from a protein of E6 or E7 of HPV 16 or HPV 18.

The teachings of Schoolnik et al. anticipates the claimed invention by disclosing a peptide from a HPV protein wherein the peptide binds to a MHC Class I molecule, and a

method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition. The compositions and methods disclosed in Schoolnik et al. are believed to inherently possess properties which anticipates the claimed invention or if they are not the same the composition and methods, the HPV peptides (and compositions) and methods of treatment as disclosed by Schoolnik et al. would none the less render the claims obvious because it possesses the components necessary to prepare a peptide from HPV and methods of treatment as claimed in the instant application. Binding of MHC Class I molecules via T-cell activation is an inherent part of the process of generating an immunogenic response in a mammal. Since the Office does not have the facilities for examining and comparing applicants' method for preparation of a HPV peptide and methods of treatment of the prior art, the burden is on applicant to show a novel or unobvious differences between the claimed product and the product of the prior art (i.e., that the peptide, composition, and method of use of the prior art does not possess the same material structural and functional characteristics of the claimed composition and methods of preparation). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

In response to Applicant's argument that Schoolnik et al. does not include certain features of Applicant's invention, the limitations on which the Applicant relies (i.e., peptides have to fit snugly in the groove of HLA Class I molecule; pockets in the groove; specific anchor residues) are not stated in the claims. Therefore, it is irrelevant whether the reference includes those features or not.

It is noted that the use of prior art published after Applicants' effective filing date can not be used rebut rejections.

Applicant's arguments filed February 26, 1996 have been fully considered but they are not deemed to be persuasive.

Applicants' comments have been addressed previously. Applicants directed the Examiner to the previous response. It is noted at p. 11 of the previous response that

Applicants stated "... one was demonstrated by applicants not to have the binding ability to HLA molecule which is a prerequisite to be a CTL epitope...". Evidence to support Applicants' assertion that the prior art does not anticipated or obviate the claimed invention should be submitted in the form of a declaration.

21. The following new rejection has not been necessitated by the amendment.

22. Claims 2, 4-18 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 and its dependent claims are vague and indefinite in the recitation of "comprising" as the use of the open-ended term "comprises" which fails to exclude unrecited steps and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d.522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). Claim 25 is directed to a peptide comprising an amino acid sequence derived from a HPV protein wherein the sequence comprises a nonapeptide from E6 or E7 of HPV 16 or HPV 18. Claim 9 is indefinite and lacks proper antecedent basis in that the claim depends from claim 1 which has been cancelled.

23. No claims are allowed.

24. Applicant's amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT

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MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is (703) 305-3394. The examiner can normally be reached on Monday-Thursday from 7:00 AM-4:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

N. M. Minnifield
May 31, 1996

James C. Housel 6/10/96
JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER
GROUP 100

FORM PTO-892 (REV. 2-92) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
8/170844	1802	16

APPLICANT(S) KAST ETAL.

NOTICE OF REFERENCES CITED

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
A						
B						
C						
D						
E						
F						
G						
H						
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K						

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
L								
M								
N								
O								
P								
Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R Bevier et al. 1990. Science 247: 1306-1310.

S Hoogstemmetal. 1986. Vaccine 8 6 pp. 21-25.

Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/170,344	03/30/94	KAST	W D4513TFM

EXAMINER: MISHRIKY, FIELD, M

ART UNIT	PAPER NUMBER
1802	16

DATE MAILED: 06/14/96

16M1/0614

COOPER & DUNHAM
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

Responsive to communication(s) filed on 2-26-96

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- [X] Claim(s) 2, 4-18, 25 is/are pending in the application.
- [ ] Of the above, claim(s) _____ is/are withdrawn from consideration.
- [ ] Claim(s) _____ is/are allowed.
- [X] Claim(s) 2, 4-18, 25 is/are rejected.
- [ ] Claim(s) _____ is/are objected to.
- [ ] Claim(s) _____ are subject to restriction or election requirement.

Application Papers

- [ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- [ ] The drawing(s) filed on _____ is/are objected to by the Examiner.
- [ ] The proposed drawing correction, filed on _____ is [ ] approved [ ] disapproved.
- [ ] The specification is objected to by the Examiner.
- [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
  - [ ] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been
    - [ ] received.
    - [ ] received in Application No. (Series Code/Serial Number) _____
    - [ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- [X] Notice of Reference Cited, PTO-892
- [X] Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- [ ] Interview Summary, PTO-413
- [ ] Notice of Draftsperson's Patent Drawing Review, PTO-948
- [ ] Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

* U.S. GPO: 1995-405-390/45

08/770344 Driefjord

INITIALS

ABANDONED [redacted]

Date Entered or Counted

Date Received or Mailed

RECEIVED JUN 14 1994 GROUP 1800

1.	Application papers.	30 Nov. 1994
2.	Declaration	04 April 1994
3.	IDS	02 MAY 1994
4.		5/17/94
5.		
6.		
7.		
8.		9/1/94
9.	Raw Sequence Listing (CRF)	4/7/95
10.	Key Ferme 3 mo	7/7/95
11.	Amendt C	3/15/95
12.	Suppl. Response	8-08-95 8/21
13.	Rejection 3 mo	2-21-96
14.		2-21-96 2/23
15.	Amdt D	6-14-96 6/10
16.	Key Ferme	1/23/97
17.	Notice of Abandonment	3/10/04
18.	Power to Inspect	
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LOCATION:+2123910525 RX TIME 17.03.'04 21:18

Den Haag • Groningen • Arnhem • 's-Hertogenbosch • Amersfoort • Nijmegen

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Merkengemachtigden
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Postbus 151
3720 AD Bilthoven

Uw ref.
Onze ref. ME/P20884US00

Amersfoort,
23 maart 2004

Betr.: Octrooiaanvrage in de V.S. van Amerika nr. 08/170,344
"HPV-V"

Geachte heer/mevrouw,

Inzake bovengenoemde octrooiaanvrage zend ik u hierbij de laatste missive van de Amerikaanse Octrooiraad. Mocht u hierover echter vragen hebben, dan verneem ik deze gaarne van u.

Een antwoord kan worden ingediend op of vóór 5 april 2004. Van deze termijn is uitstel te verkrijgen.

Ik verzoek u mij uw instructies, voor het beantwoorden van de openstaande missive, zo spoedig mogelijk te doen toekomen.

Met vriendelijke groet,
VEREENIGDE

M. Einerhand

Bijl.: als genoemd

Cc.: Leids Universitair Medisch Centrum, Prof. Dr. C.J.M. Melief

ne

Exhibit F

Elst van der N.

From: Einerhand M.
Sent: donderdag 8 april 2004 19:02
To: 'sdavis@cooperdunham.com'
Cc: Elst van der N.
Subject: your ref 45113 our ref ME -20884us00

Dear mr Katz accompanying please find a discussion peace for drafting a response to the office action in the case identified above.

Please review the letter and provide me with your comments and suggestions for moving forward in this case. I have also included comments from the inventor melief on the office action.

Sincerely,

Mark Einerhand

039 Einerhand.doc

Concept antwoord op Office act...

Exhibit G

Den Haag • Groningen • Arnhem • 's-Hertogenbosch • Amersfoort • Nijmegen

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Your ref. yourref
Our ref. ourref

Den Haag,
date

Re:

Dear mr. Katz,

This is in response to the Office Action that you faxed us on March 17, 2004. I would like to ask your opinion on the following matters.

The Office Action was signed by the supervisory patent examiner James Housel on June 10, 1996. You mentioned on the phone that the patent application became abandoned as result of not responding to this Office Action. I presume therefore that the application became abandoned in December 1996. You mentioned that you would provide us with details as to what events led to the abandonment. However, we have as yet not received this information. We urge you again to provide us with the information as soon as possible.

In the meantime, the client wishes to revive the application. Considering the interest of the applicant in this matter and the fact that the application is licensed I request that you vigorously pursue the actions to be taken in this file.

The Office Action is final, implying that we have limited possibilities to argue the patentability of the claims. However, from your colleague mr. Gershik I learned that it should be possible to remove the finality of the Office Action under rule 1.129. In view of this possibility I suggest that we pursue the claims listed in the appendix.

You will notice that this claim set differs from the last claim set only in that claims 17 and 18 have been cancelled. We propose this strategy in view of the fact that whereas all claims were rejected under 35 U.S.C. § 112, first paragraph (lack of an enabling

disclosure), the arguments of the examiner are solely based on the pharmaceutical composition claims. For this reason it is suggested that we cancel two of the three pharmaceutical composition claims and provide detailed argumentation for enablement of the remaining pharmaceutical composition claim. As mentioned above, the peptide claims are formally rejected. However, the examiner provides no specific arguments against the peptide claim of 25 other than the sentence on page 3 wherein it is said that the disclosure is enabled for nonapeptide sequences derived from the E6 or E7 genes of HPV16 or HPV18, and MHC Class I molecules specifically taught in the specification. Could we limit our argumentation on the peptide claims to a discussion of the sentence on page 5, third paragraph, where the examiner states that the wording "peptides that bind in the groove on an MHC class I molecule" is not present in the claims? Claim 25 appears to contain this requirement.

The rejection of the pharmaceutical claims is quite extensive but seems to boil down to the now cancelled claims 17 and 18. The broadest pharmaceutical claim 16 is in my view defendable. There are two possibilities that I would like to put forward for your review. The first option is to leave the claim as it is. The other option is to cancel the phrase "a prophylactically or therapeutically effective amount" and replace it with "an effective amount". The argument for enablement is that peptides that bind to MHC-I are always capable of eliciting a cellular immune response of the peptide when present in an effective amount. That is the way the immune system works, it mounts an immune response to peptides that are presented in the context of MHC-I. Whether the immune response is sufficient to be effective against HPV (the requirement of claims 17 and 18) is in this strategy no longer a question as we do not require such effectiveness in our claims. If you can support this approach I can obtain art that underlines these arguments from the inventors.

The examiner objects to the phrase "fragments, homologs, isoforms, derivatives, genetic variants or conservative variants" in claims 5, 6, 8, 10, 12 and 14. I suggest that we cancel this phrase and replace it with the phrase "or a variant of any one of these amino acid sequences differing by one conservative amino acid substitution". Basis for this amendment can be found on page 17, lines 5-12 and example 4: page 31, lines 26-34 and table IX to XIII on pages 32-35. The examples show that such peptides were generated in the application and are effective in binding to MHC-class I molecules.

Please take care of the minor amendment of claims 12 and 14, writing the selection in the proper markush format. Apparently the examiner could not properly identify which "or" was to be replaced by an "and"

With respect to Schoolnik et al, it appears as if the examiner mixes up antibody immunity and cellular immunity. These two types of immunity are generated through different systems. For cellular immunity to be developed against a peptide it is

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essential that the peptide is presented in the context of MHC class I. Schoolnik provides at best a means for developing a humeral response.

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Attorneys-at-Law
VEREENIGDE

Appendix

Claims

25. (Rewritten, cancelled claim 1) A peptide comprising an amino acid sequence derived from protein of human papilloma virus (HPV), wherein said amino acid sequence comprises a nonapeptide derived from protein E6 or E7 of HPV or HPV 18 and wherein said nonapeptide has the ability to bind in the grooves on top of the human major histocompactability complex (MHC) Class I molecule.

2. A peptide according to claim 25, wherein said amino acid sequence is a nonapeptide.

4. A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1.

5. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
KLPQLCTEL (residues 18-26 of HPV16 protein E6) SEQ ID NO:2
QLCTELQTT (residues 21-29 of HPV16 protein E6) SEQ ID NO:3
LCTELQTTI (residues 22-30 of HPV16 protein E6) SEQ ID NO:4
ELQTTIHDI (residues 25-33 of HPV16 protein E6) SEQ ID NO:5
LQTTIHDII (residues 26-34 of HPV16 protein E6) SEQ ID NO:6
TIHDIILEC (residues 29-37 of HPV16 protein E6) SEQ ID NO:7
IHDIILECV (residues 30-38 of HPV16 protein E6) SEQ ID NO:8
CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
FAFRDLCIV (residues 52-60 of HPV16 protein E6) SEQ ID NO:10
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
PLCDLLIRC (residues 102-110 of HPV16 protein E6) SEQ ID NO:12
TLHEYMLDL (residues 7-15 of HPV16 protein E7) SEQ ID NO:13
YMLDLQPET (residues 11-19 of HPV16 protein E7) SEQ ID NO:14
MLDLQPETT (residues 12-20 of HPV16 protein E7) SEQ ID NO:15
RLCVQSTHV (residues 66-74 of HPV16 protein E7) SEQ ID NO:16
TLEDLLMGT (residues 78-86 of HPV16 protein E7) SEQ ID NO:17
LLMGTLGIV (residues 82-90 of HPV16 protein E7) SEQ ID NO:18

Exhibit H

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Attorneys-at-Law

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GTLGIVCPI (residues 85-93 of HPV16 protein E7) SEQ ID NO:19 and
TLGIVCPIC (residues 86-94 of HPV16 protein E7) SEQ ID NO:20
or a variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-A2.1.

6. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV18, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1 and is selected from the group consisting of:

KLPDLCTEL (residues 13-21 of HPV18 protein E6) SEQ ID NO:21
SLQDIEITC (residues 24-32 of HPV18 protein E6) SEQ ID NO:22
LQDIEITCV (residues 25-33 of HPV18 protein E6) SEQ ID NO:23
EITCVYCKT (residues 29-37 of HPV18 protein E6) SEQ ID NO:24
KTVLELTEV (residues 36-44 of HPV18 protein E6) SEQ ID NO:25
ELTEVFEFA (residues 40-48 of HPV18 protein E6) SEQ ID NO:26
FAFKDLFVV (residues 47-55 of HPV18 protein E6) SEQ ID NO:27
DTLEKLTNT (residues 88-96 of HPV18 protein E6) SEQ ID NO:28
LTNTGLYNL (residues 93-101 of HPV18 protein E6) SEQ ID NO:29
TLQDIVLHL (residues 7-15 of HPV18 protein E7) SEQ ID NO:30
FQQLFLNTL (residues 86-94 of HPV18 protein E7) SEQ ID NO:31
QLFLNTLSF (residues 88-96 of HPV18 protein E7) SEQ ID NO:32
LFLNTLSFV (residues 89-97 of HPV18 protein E7) SEQ ID NO:33 and
LSFVCPWCA (residues 94-102 of HPV18 protein E7) SEQ ID NO:34, and
or a variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-A2.1.

7. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A1.

8. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 and E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A1 and is selected from the group consisting of:

YRDGNPYAV (residues 61-69 of HPV16 protein E6) SEQ ID NO:35
WTGRCMSCC (residues 139-147 of HPV16 protein E6) SEQ ID NO:36
MSCCRSSRT (residues 144-152 of HPV16 protein E6) SEQ ID NO:37
TTDLYCYEQ (residues 19-27 of HPV16 protein E7) SEQ ID NO:38
EIDGPAGQA (residues 37-45 of HPV16 protein E7) SEQ ID NO:39 and
HVDIRTLED (residues 73-81 of HPV16 protein E7) SEQ ID NO:40, and

or a variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-A3.2.

9. A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human to human MHC Class I allele HLA-A3.2.

10. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A3.2 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
IILECVYCK (residues 33-41 of HPV16 protein E6) SEQ ID NO:41
CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO:42
QQLLRREVY (residues 42-50 of HPV16 protein E6) SEQ ID NO:43
IVYRDGNPY (residues 59-67 of HPV16 protein E6) SEQ ID NO:44
YAVCDKCLK (residues 67-75 of HPV16 protein E6) SEQ ID NO:45
AVCDKCLKF (residues 68-76 of HPV16 protein E6) SEQ ID NO:46
VCDKCLKFY (residues 69-77 of HPV16 protein E6) SEQ ID NO:47
KFYSKISEY (residues 75-83 of HPV16 protein E6) SEQ ID NO:48
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
ISEYRHYCY (residues 80-88 of HPV16 protein E6) SEQ ID NO:49
RHYCYSLYG (residues 84-92 of HPV16 protein E6) SEQ ID NO:50
SLYGTTLEQ (residues 89-97 of HPV16 protein E6) SEQ ID NO:51
TTLEQQYNK (residues 93-101 of HPV16 protein E6) SEQ ID NO:52
QQYNKPLCD (residues 97-105 of HPV16 protein E6) SEQ ID NO:53
LIRCINCQK (residues 107-115 of HPV16 protein E6) SEQ ID NO:54
HLDKKQRFH (residues 125-133 of HPV16 protein E6) SEQ ID NO:55
CMSCCRSSR (residues 143-151 of HPV16 protein E6) SEQ ID NO:56
SCCRSSRTR (residues 145-153 of HPV16 protein E6) SEQ ID NO:57
CCRSSRTRR (residues 146-154 of HPV16 protein E6) SEQ ID NO:58
HYNIVTFCC (residues 51-59 of HPV16 protein E7) SEQ ID NO:59
YNIVTFCCK (residues 52-60 of HPV16 protein E7) SEQ ID NO:60
CCKCDSTLR (residues 58-66 of HPV16 protein E7) SEQ ID NO:61 and
KCDSTLRLC (residues 60-68 of HPV16 protein E7) SEQ ID NO:62, and

or a variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-All.2.

11. A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-All.2.

12. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-All.2 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
IILECVYCK (residues 33-41 of HPV16 protein E6) SEQ ID NO:41
CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO:42
QQLLRREVY (residues 42-50 of HPV16 protein E6) SEQ ID NO:43
IVYRDGNPY (residues 59-67 of HPV16 protein E6) SEQ ID NO:44
YAVCDKCLK (residues 67-75 of HPV16 protein E6) SEQ ID NO:45
AVCDKCLKF (residues 68-76 of HPV16 protein E6) SEQ ID NO:46
VCDKCLKFY (residues 69-77 of HPV16 protein E6) SEQ ID NO:47
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
ISEYRHYCY (residues 80-88 of HPV16 protein E6) SEQ ID NO:49
LIRCINCQK (residues 107-115 of HPV16 protein E6) SEQ ID NO:54
TGRCMSCCR (residues 140-148 of HPV16 protein E6) SEQ ID NO:63
CMSCCRSSR (residues 143-151 of HPV16 protein E6) SEQ ID NO:56
SCCRSSRTR (residues 145-153 of HPV16 protein E6) SEQ ID NO:57
HYNIVTFCC (residues 51-59 of HPV16 protein E7) SEQ ID NO:59
YNIVTFCCK (residues 52-60 of HPV16 protein E7) SEQ ID NO:60
CCKCDSTLR (residues 58-66 of HPV16 protein E7) SEQ ID NO:61 and
VCPICSQKP (residues 90-98 of HPV16 protein E7) SEQ ID NO:64 and
or a variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-All.2..

13. A peptide according to claim 25, wherein said amino acid sequence to bind to human MHC Class I allele HLA-A24.

14. A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A24 and is selected from the group consisting of:

MHQKRTAMF (residues 1-9 of HPV16 protein E6) SEQ ID NO:65
LQTTIHDII (residues 26-34 of HPV16 protein E6) SEQ ID NO:6
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO42:
LLRREVYDF (residues 44-52 of HPV16 protein E6) SEQ ID NO:66
VYDFAFRDL (residues 49-57 of HPV16 protein E6) SEQ ID NO:67
PYAVCDKCL (residues 66-74 of HPV16 protein E6) SEQ ID NO:68

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KCLKFYSKI (residues 72-80 of HPV16 protein E6) SEQ ID NO:69
EYRHYCYSL (residues 82-90 of HPV16 protein E6) SEQ ID NO:70
HYCYSLYGT (residues 85-93 of HPV16 protein E6) SEQ ID NO:71
CYSLYGTTL (residues 87-95 of HPV16 protein E6) SEQ ID NO:72
RFHNIRGRW (residues 131-139 of HPV16 protein E6) SEQ ID NO:73 and
RAHYNIVTF (residues 49-57 of HPV16 protein E7) SEQ ID NO:74, and
or a variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-A24.

15. A peptide according to claim 25, having a length of from 9 to 12 amino acids.

16. A pharmaceutical composition containing a prophylactically or therapeutically effective amount for eliciting cellular immune response of a peptide according to claim 25, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

Den Haag • Groningen • Arnhem • 's-Hertogenbosch • Amersfoort • Nijmegen

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Postbus 151
3720 AD Bilthoven

Attn. Mr. W.J.M. de Vette

Your ref.
Our ref. ME/P20884US00

Den Haag,
April 29, 2004

Re: U.S. patent application No. 08/170,344
"HPV-V"

Dear Mr. De Vette,

I have enclosed the proposal from Cooper & Dunham for reinstating application number 08/170,344. The proposal encompasses four items, the petition to revive, the response to the Office Action, a request to withdraw the finality of the Office Action and a terminal disclaimer. I have given a short description of the documents together with some comments on substantive response to the Office Action below.

The petition to revive contains the statement that the abandonment of the application was unintentional. The statement does not elaborate on the circumstances that have led to the abandonment. As discussed in our telephone conversation of today, Vereenigde will send a reminder to Cooper & Dunham that we are still waiting for an explanation of the events that have led to the abandonment. I noticed that the petition requires the payment of a fee. The proposal did not come with an explanation that Cooper & Dunham will pay this fee. I will point them to the fact that we expect that any costs associated with the revival will be taken care of by Cooper & Dunham.

The proposal further contains a request to remove the finality of the Office Action. The request will, according to Cooper & Dunham, have the effect that we will have at least one more opportunity to argue patentability of the claims and/or file amendments.

Exhibit I

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Attorneys-at-Law
VEREENIGDE

The enclosed terminal disclaimer is necessary to disclaim the period of abandonment.

The response to the Office Action is more or less in line with the strategy that we discussed earlier. The amendments to the claims have been kept to a minimum. A first amendment is concerned with the pharmaceutical composition claims 16-18. A large part of the objections of the examiner is concerned with these claims. The examiner is of the opinion that the specification does not support the breadth of the claims because it lacks working examples or support for *in vivo* efficacy of the active ingredients. The suggested amendment is intended to circumvent this objection of the examiner in that such efficacy is no longer a part of the claims. This is done by deleting claims 17 and 18 and broadening claim 16 such that a prophylactically or therapeutically effective amount is no longer required but instead requires only an amount effective in obtaining a cellular immune response. In my estimation this amendment should be sufficient to remove the lack of support rejection against claim 16, as to my best knowledge any peptide capable of binding to MHC-I, is able to elicit such a cellular immune response when provided in sufficient amounts to a human carrying the specific MHC-I molecule.
A further amendment is in claims 5, 6, 8, 10, 12, and 14 and is concerned with the deletion of the phrase "fragments, homologues, isoforms, derivatives, genetic variants or conservative variants" and replacing it with the phrase "or a variant of any one of these amino acid sequences differing by one conservative amino acid substitution". This amendment is instigated by the experience that it is difficult to convince examiners of the patentability of the deleted subject matter, in the absence of support in the specification. Moreover, fragments of the nona-peptides will more than likely not be effective, whereas isoforms are already included in the structural formula of the sequence. The sentence replacing the deletion covers peptides that deviate by one conservative amino acid from the depicted peptide. Example 4 shows peptides comprising a replacement of a cysteine.
A further amendment deals with a correction of improper language of claims 12 to 14.

Considering that the present situation is exceptional we will independently and at our own expense obtain a second opinion from a US patent attorney with respect to the actions to be taken in this case. Particularly we will request clarification of the, as yet, conflicting opinions maintained by the lawyers of the licensee and Cooper & Dunham as to the required declarations for requesting revival of the application.

Patent Attorneys
Trademark Attorneys
Attorneys-at-Law

VEREENIGDE

Please do not hesitate to contact me if you have questions regarding the actions to be taken or the proposal from Cooper & Dunham.

Sincerely,
VEREENIGDE

Mark Einerhand

Encl: Draft Petition to revive
Draft Response to Office Action
Draft Request for removal of the finality of the Office Action
Draft Terminal Disclaimer

Dkt. 45113/RDK/AG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Wybe Martin Kast et al.

Serial No. : 08/170,344 Examiner: N. Minnifield

Filed : March 30, 1994

For : PEPTIDES OF HUMAN PAPILLOMA VIRUS FOR USE IN HUMAN T CELL RESPONSE INDUCING COMPOSITIONS

1185 Avenue of the Americas
New York, NY 10036
April 20, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

COMMUNICATION REQUESTING WITHDRAWAL OF FINALITY UNDER 37 C.F.R. §1.129(a)

This Communication is submitted pursuant to the provisions of 37 C.F.R. §1.129(a) to request withdrawal of the finality of the June 14, 1996 Final Office Action issued by the U.S. Patent and Trademark Office in connection with the above-identified application. Applicants request consideration of the First Submission Under 37 C.F.R. § 1.129(a) and Amendment in Response to June 14, 1996 Final Office Action attached hereto as **Exhibit A.**

The subject application has been pending for at least two years as of June 8, 1995, taking into account reference made to earlier filed applications under 35 U.S.C. §§120, 121, and 365(c).

Under 37 C.F.R. §1.129(a), applicants in an application that has been pending for at least two years as of June 8, 1995, taking into account any reference made in such application to any earlier filed application under 35 U.S.C. §§120, 121 and 365(c), are entitled to have the finality of a final rejection withdrawn and a submission entered and considered on the merits twice after final rejection if the submission and the fee set forth in 37 C.F.R. §1.17(r) are filed prior to the filing of an appeal brief and

Exhibit J

prior to abandonment of the application.

The fee for a large entity under 37 C.F.R. §1.17(r) for consideration and entry of a first submission after a final rejection is SEVEN-HUNDRED AND SEVENTY DOLLARS ($770.00) and a check for TWO THOUSAND ONE HUNDRED DOLLARS ($2,100.00) which includes this amount is enclosed.

Applicants respectfully request, pursuant to 37 C.F.R. §1.129(a), to have the finality of the June 14, 1996 Final Office Action withdrawn and to have their first submission entered and considered on the merits in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided.

No fee, other than the $770.00 fee under 37 C.F.R. §1.17(r) is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Robert D. Katz
Reg. No. 30,141

Date

Robert D. Katz, Esq.
Registration No. 30,141
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036
(212) 278-0400

Dkt. 45113/RDK/AG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Wybe Martin Kast et al.	
Serial No.	:	08/170,344	Examiner: N. Minnifield
Filed	:	March 30, 1994	
For	:	PEPTIDES OF HUMAN PAPILLOMA VIRUS FOR USE IN HUMAN T CELL RESPONSE INDUCING COMPOSITIONS	

1185 Avenue of the Americas
New York, NY 10036
April 20, 2004

Office of Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

PETITION TO REVIVE UNINTENTIONALLY ABANDONED APPLICATION UNDER 37 C.F.R. §1.137(b)

This petition is made in response to the January 23, 1997 Notice of Abandonment issued in connection with the above-identified application. Applicants understand that no reply to the June 14, 1996 Final Office was filed resulting in abandonment.

Applicants hereby petition to revive the subject abandoned application pursuant to 37 C.F.R. §1.137(b). A grantable petition under this paragraph must be accompanied by (1) the reply required to the outstanding Office action or notice, unless previously filed; (2) the petition fee as set forth in §1.17(m); (3) a statement that the entire delay in filing the required reply from the due date for the reply until the filing of a grantable petition pursuant to this paragraph was unintentional; and (4) any terminal disclaimer required pursuant to 37 C.F.R. §1.137(d).

In satisfaction of the requirements for a grantable petition under 37 C.F.R. §1.137(b), applicants have enclosed as **Exhibit A** the required reply to the June 14, 1996 Final

Exhibit K

Office Action issued in connection with this application. Applicants submit that the entire delay in filing this reply from the due date for the reply until the filing of this petition was unintentional. The fee to revive an unintentionally abandoned application required under 37 C.F.R. §1.137(b) is ONE THOUSAND THREE HUNDRED THIRTY DOLLARS ($1330.00) and a check for TWO THOUSAND ONE HUNDRED DOLLARS ($2,100.00) which includes this amount is enclosed.

In addition, applicants submit as **Exhibit B** a terminal disclaimer as required under 37 C.F.R. §1.137(d) in connection with the filing of this petition.

No fee, other than the enclosed $1330.00, is deemed necessary in connection with the filing of this Petition. However, if any other fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Robert D. Katz Date
Reg. No. 30,141

Robert D. Katz, Esq.
Registration No. 30,141
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036
(212) 278-0400

Dkt. 45113/RDK/AG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Wybe Martin Kast et al.

Serial No. : 08/170,344 Examiner: N. Minnifield

Filed : March 30, 1994

For : PEPTIDES OF HUMAN PAPILLOMA VIRUS FOR USE IN HUMAN T CELL RESPONSE INDUCING COMPOSITIONS

1185 Avenue of the Americas
New York, NY 10036
April 21, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT IN RESPONSE TO JUNE 14, 1996 FINAL OFFICE ACTION

This Amendment is submitted in response to a June 14, 1996 Final Office Action issued by the United States Patent and Trademark Office in connection with the above-identified application. This Response forms part of a Petition to Revive an Unintentionally Abandoned Application under 37 C.F.R. §1.137(b). Applicants also file herewith a Communication Requesting Withdrawal of Finality under 37 C.F.R. §1.129(a). Revival of the application and examination of the present response is respectfully requested.

Please amend the subject application as follows:

Exhibit L

Amendments to the claims:

The following listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims:

1. (canceled)

2. (previously presented) A peptide according to claim 25, wherein said amino acid sequence is a nonapeptide.

3. (canceled)

4. (previously presented) A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1.

5. (amended) A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
KLPQLCTEL (residues 18-26 of HPV16 protein E6) SEQ ID NO:2
QLCTELQTT (residues 21-29 of HPV16 protein E6) SEQ ID NO:3
LCTELQTTI (residues 22-30 of HPV16 protein E6) SEQ ID NO:4
ELQTTIHDI (residues 25-33 of HPV16 protein E6) SEQ ID NO:5
LQTTIHDII (residues 26-34 of HPV16 protein E6) SEQ ID NO:6

TIHDIILEC (residues 29-37 of HPV16 protein E6) SEQ ID NO:7
IHDIILECV (residues 30-38 of HPV16 protein E6) SEQ ID NO:8
CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
FAFRDLCIV (residues 52-60 of HPV16 protein E6) SEQ ID NO:10
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
PLCDLLIRC (residues 102-110 of HPV16 protein E6) SEQ ID NO:12
TLHEYMLDL (residues 7-15 of HPV16 protein E7) SEQ ID NO:13
YMLDLQPET (residues 11-19 of HPV16 protein E7) SEQ ID NO:14
MLDLQPETT (residues 12-20 of HPV16 protein E7) SEQ ID NO:15
RLCVQSTHV (residues 66-74 of HPV16 protein E7) SEQ ID NO:16
TLEDLLMGT (residues 78-86 of HPV16 protein E7) SEQ ID NO:17
LLMGTLGIV (residues 82-90 of HPV16 protein E7) SEQ ID NO:18
GTLGIVCPI (residues 85-93 of HPV16 protein E7) SEQ ID NO:19
TLGIVCPIC (residues 86-94 of HPV16 protein E7) SEQ ID NO:20 and
a ~~fragment, homolog, isoform, derivative, genetic variant or conservative~~ variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-A2.1.

6. (amended) A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV18, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A2.1 and is selected from the group consisting of:

KLPDLCTEL (residues 13-21 of HPV18 protein E6) SEQ ID NO:21
SLQDIEITC (residues 24-32 of HPV18 protein E6) SEQ ID NO:22
LQDIEITCV (residues 25-33 of HPV18 protein E6) SEQ ID NO:23
EITCVYCKT (residues 29-37 of HPV18 protein E6) SEQ ID NO:24

KTVLELTEV (residues 36-44 of HPV18 protein E6) SEQ ID NO:25
ELTEVFEFA (residues 40-48 of HPV18 protein E6) SEQ ID NO:26
FAFKDLFVV (residues 47-55 of HPV18 protein E6) SEQ ID NO:27
DTLEKLTNT (residues 88-96 of HPV18 protein E6) SEQ ID NO:28
LTNTGLYNL (residues 93-101 of HPV18 protein E6) SEQ ID NO:29
TLQDIVLHL (residues 7-15 of HPV18 protein E7) SEQ ID NO:30
FQQLFLNTL (residues 86-94 of HPV18 protein E7) SEQ ID NO:31
QLFLNTLSF (residues 88-96 of HPV18 protein E7) SEQ ID NO:32
LFLNTLSFV (residues 89-97 of HPV18 protein E7) SEQ ID NO:33
LSFVCPWCA (residues 94-102 of HPV18 protein E7) SEQ ID NO:34 and
a ~~fragment, homolog, isoform, derivative, genetic variant or conservative~~ variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-A2.1.

7. (previously presented) A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A1.

8. (amended) A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 and E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A1 and is selected from the group consisting of:

YRDGNPYAV (residues 61-69 of HPV16 protein E6) SEQ ID NO:35
WTGRCMSCC (residues 139-147 of HPV16 protein E6) SEQ ID NO:36
MSCCRSSRT (residues 144-152 of HPV16 protein E6) SEQ ID NO:37
TTDLYCYEQ (residues 19-27 of HPV16 protein E7) SEQ ID NO:38

EIDGPAGQA (residues 37-45 of HPV16 protein E7) SEQ ID NO:39
HVDIRTLED (residues 73-81 of HPV16 protein E7) SEQ ID NO:40 and
a ~~fragment, homolog, isoform, derivative, genetic variant or conservative~~ variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-A3.2.

9. (previously presented) A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human to human MHC Class I allele HLA-A3.2.

10. (amended) A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-A3.2 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
IILECVYCK (residues 33-41 of HPV16 protein E6) SEQ ID NO:41
CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO:42
QQLLRREVY (residues 42-50 of HPV16 protein E6) SEQ ID NO:43
IVYRDGNPY (residues 59-67 of HPV16 protein E6) SEQ ID NO:44
YAVCDKCLK (residues 67-75 of HPV16 protein E6) SEQ ID NO:45
AVCDKCLKF (residues 68-76 of HPV16 protein E6) SEQ ID NO:46
VCDKCLKFY (residues 69-77 of HPV16 protein E6) SEQ ID NO:47
KFYSKISEY (residues 75-83 of HPV16 protein E6) SEQ ID NO:48
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
ISEYRHYCY (residues 80-88 of HPV16 protein E6) SEQ ID NO:49

RHYCYSLYG (residues 84-92 of HPV16 protein E6) SEQ ID NO:50
SLYGTTLEQ (residues 89-97 of HPV16 protein E6) SEQ ID NO:51
TTLEQQYNK (residues 93-101 of HPV16 protein E6) SEQ ID NO:52
QQYNKPLCD (residues 97-105 of HPV16 protein E6) SEQ ID NO:53
LIRCINCQK (residues 107-115 of HPV16 protein E6) SEQ ID NO:54
HLDKKQRFH (residues 125-133 of HPV16 protein E6) SEQ ID NO:55
CMSCCRSSR (residues 143-151 of HPV16 protein E6) SEQ ID NO:56
SCCRSSRTR (residues 145-153 of HPV16 protein E6) SEQ ID NO:57
CCRSSRTRR (residues 146-154 of HPV16 protein E6) SEQ ID NO:58
HYNIVTFCC (residues 51-59 of HPV16 protein E7) SEQ ID NO:59
YNIVTFCCK (residues 52-60 of HPV16 protein E7) SEQ ID NO:60
CCKCDSTLR (residues 58-66 of HPV16 protein E7) SEQ ID NO:61
KCDSTLRLC (residues 60-68 of HPV16 protein E7) SEQ ID NO:62 and
a ~~fragment, homolog, isoform, derivative, genetic variant or conservative~~ variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-All.2.

11. (previously presented) A peptide according to claim 25, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-All.2.

12. (amended) A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has the ability to bind to human MHC Class I allele HLA-All.2 and is selected from the group consisting of:

AMFQDPQER (residues 7-15 of HPV16 protein E6) SEQ ID NO:1
IILECVYCK (residues 33-41 of HPV16 protein E6) SEQ ID NO:41

CVYCKQQLL (residues 37-45 of HPV16 protein E6) SEQ ID NO:9
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO:42
QQLLRREVY (residues 42-50 of HPV16 protein E6) SEQ ID NO:43
IVYRDGNPY (residues 59-67 of HPV16 protein E6) SEQ ID NO:44
YAVCDKCLK (residues 67-75 of HPV16 protein E6) SEQ ID NO:45
AVCDKCLKF (residues 68-76 of HPV16 protein E6) SEQ ID NO:46
VCDKCLKFY (residues 69-77 of HPV16 protein E6) SEQ ID NO:47
KISEYRHYC (residues 79-87 of HPV16 protein E6) SEQ ID NO:11
ISEYRHYCY (residues 80-88 of HPV16 protein E6) SEQ ID NO:49
LIRCINCQK (residues 107-115 of HPV16 protein E6) SEQ ID NO:54
TGRCMSCCR (residues 140-148 of HPV16 protein E6) SEQ ID NO:63
CMSCCRSSR (residues 143-151 of HPV16 protein E6) SEQ ID NO:56
SCCRSSRTR (residues 145-153 of HPV16 protein E6) SEQ ID NO:57
HYNIVTFCC (residues 51-59 of HPV16 protein E7) SEQ ID NO:59
YNIVTFCCK (residues 52-60 of HPV16 protein E7) SEQ ID NO:60
CCKCDSTLR (residues 58-66 of HPV16 protein E7) SEQ ID NO:61
VCPICSQKP (residues 90-98 of HPV16 protein E7) SEQ ID NO:64 and
a ~~fragment, homolog, isoform, derivative, genetic variant or conservative~~ variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-All.2.

13. (previously presented) A peptide according to claim 25, wherein said amino acid sequence to bind to human MHC Class I allele HLA-A24.

14. (amended) A peptide according to claim 25, comprising an amino acid sequence derived from protein E6 or E7 of HPV16, wherein said amino acid sequence has

the ability to bind to human MHC Class I allele HLA-A24 and is selected from the group consisting of:

MHQKRTAMF (residues 1-9 of HPV16 protein E6) SEQ ID NO:65
LQTTIHDII (residues 26-34 of HPV16 protein E6) SEQ ID NO:6
VYCKQQLLR (residues 38-46 of HPV16 protein E6) SEQ ID NO42:
LLRREVYDF (residues 44-52 of HPV16 protein E6) SEQ ID NO:66
VYDFAFRDL (residues 49-57 of HPV16 protein E6) SEQ ID NO:67
PYAVCDKCL (residues 66-74 of HPV16 protein E6) SEQ ID NO:68
KCLKFYSKI (residues 72-80 of HPV16 protein E6) SEQ ID NO:69
EYRHYCYSL (residues 82-90 of HPV16 protein E6) SEQ ID NO:70
HYCYSLYGT (residues 85-93 of HPV16 protein E6) SEQ ID NO:71
CYSLYGTTL (residues 87-95 of HPV16 protein E6) SEQ ID NO:72
RFHNIRGRW (residues 131-139 of HPV16 protein E6) SEQ ID NO:73
RAHYNIVTF (residues 49-57 of HPV16 protein E7) SEQ ID NO:74 and
a ~~fragment, homolog, isoform, derivative, genetic variant or conservative~~ variant of any one of these amino acid sequences differing by one conservative amino acid substitution which has the ability to bind to human MHC Class I allele HLA-A24.

15. (previously presented) A peptide according to claim 25, having a length of from 9 to 12 amino acids.

16. (amended) A pharmaceutical composition containing ~~a prophylactically or therapeutically~~ an effective amount for eliciting cellular immune response of a peptide according to claim 25, and a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

17-24. (canceled)

25. (previously presented) A peptide comprising an amino acid sequence derived from protein of human papilloma virus (HPV), wherein said amino acid sequence comprises a nonapeptide derived from protein E6 or E7 of HPV or HPV 18 and wherein said nonapeptide has the ability to bind in the grooves on top of the human major histocompactability complex (MHC) Class I molecule.

REMARKS

Claims 2, 4-18 and 25 are pending and under examination in the subject application. By this Amendment, applicants have amended claims 5, 6, 8, 10, 12, 14 and 16 and have canceled claims 17 and 18. Accordingly, claims 2, 4-16 and 25 will be pending and under examination in the subject application upon entry of this Amendment. In view of the remarks below, applicants maintain that the Examiner's rejections have been overcome, and respectfully request that they be withdrawn.

Formalities

The Examiner states that the information disclosure statement filed January 4, 1994 fails to comply with 37 C.F.R. §1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in §1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. Specifically, the Examiner states that references EP0375555 and EP0456197 have not been considered as to the merits.

In response, (statements of relevance)

Accordingly, applicants submit that the requirements of 37 C.F.R. §1.98(a)(3) have been met and request that the Examiner withdraw the objection, consider the references, and make them of record in this application.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 2, 4-18 and 25 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such

a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As the Examiner's concedes on page 3 of the June 14, 1996 Office Action, the disclosure is enabled for the subject matter as provided in claim 25, i.e. "for nonapeptide sequences from E6 and E7 genes of HPV16 or HPV18, and MHC-I class molecules as specifically taught in the specification." Therefore, applicants understand the instant rejection to be to the pharmaceutical composition claims, i.e. claims 16-18.

In response, applicants respectfully traverse the Examiner's rejection. The test for enablement is whether one skilled in the art could, at the time of the invention, make and use the claimed invention based on the disclosure and the information known in the art without undue experimentation. Applicants maintain that the claimed invention satisfies the test for enablement, and that the Examiner has not set forth sufficient grounds for concluding otherwise.

The subject invention encompasses peptides comprising an amino acid sequence derived from protein of human papilloma virus (HPV), wherein the amino acid sequence comprises a nonapeptide derived from protein E6 or E7 of HPV or HPV 18 and wherein the nonapeptide has the ability to bind in the grooves on top of the human major histocompactability complex (MHC) Class I molecule, as well as pharmaceutical compositions comprising this nonapeptide. This invention is based, at least in part, on applicants' discovery of exact HLA class I binding peptides of HPV16 and HPV18 with CTL inducing properties.

In support of the rejection, the Examiner states that the specification does not provide sufficient evidence of a method of prophylactic or therapeutic treatment of a human with cervical carcinoma or other HPV related diseases. The Examiner further alleges that although applicants have cancelled the rejected method claims, the pharmaceutical

composition claims as written suggest the composition would be administered to a subject.

In response, but without conceding the correctness of the Examiner's rejection, applicants note that pharmaceutical composition claims 17 and 18 have been cancelled, thereby rendering the rejection to these claims moot. Applicants further note that the remaining pharmaceutical composition claim 16 has been amended to recite "an effective amount," rather than "prophylactically or therapeutically effective amount." Applicants maintain that peptides that bind to MHC-I are by definition capable of eliciting a cellular response when present. This is inherent in the workings of the immune system and well known to one skilled in the pertinent art. An immune response is automatically triggered upon presentation of a peptide by MHC-I. Accordingly, claim 16 as amended does not require a prophylactic or therapeutic effect, thereby obviating the Examiner's rejection.

The Examiner further states that the scope of claims reciting "a fragment, homolog, isoforms, derivative, genetic variant or conservative variant" is not supported by the specification as it does not disclose the general tolerance to and extent of modification, specific positions and regions of the sequence(s) which can be predictably modified, the critical regions and what variants can be made that retain the biological activity of the intact protein. In response, but without conceding the correctness of the Examiner's rejection, applicants note that claims 5, 6, 8, 10, 12 and 14 have been amended thereby obviating the Examiner's rejection.

Accordingly, applicants maintain that the specification coupled with the information known in the art clearly enables one skilled in the art to practice the claimed invention. In view of these remarks, applicants maintain that claims 2, 4-16 and 25 satisfy the

requirements of 35 U.S.C. §112, first paragraph, and submit that the rejection can be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 12 and 14 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner alleges that the claims are indefinite for being in improper Markush format.

In response, but without conceding the correctness of the Examiner's rejection, applicants note that claims 12 and 14 as amended recite the proper Markush format using the suggested phrase "selected from the group consisting of" and with the conjunction "and". Accordingly, applicants maintain that amended claims 12 and 14 particularly point out and distinctly claim the subject matter of the invention.

In view of these remarks, applicants maintain that claims 12 and 14 satisfy the requirements of 35 U.S.C. §112, second paragraph, and request that the rejection be withdrawn.

Rejection under 35 U.S.C. §102(b) and §103

The Examiner rejected claims 2, 4, 7-8, 11, 13, 15-18 and 25 under 35 U.S.C. §102(b) as allegedly anticipated by or under 35 U.S.C. §103 as allegedly obvious over Schoolnik. Specifically, the Examiner alleges that the peptides and compositions of the subject invention are disclosed in Schoolnik.

Applicants respectfully traverse the Examiner's rejection, and respectfully disagree with the Examiner's interpretation of the teachings of Schoolnik. Schoolnik teaches HPV16 E6 and E7 peptides and HPV proteins which may be used to raise antibodies for diagnostic and therapeutic purposes. The subject invention, on the other hand, provides peptides comprising an amino acid sequence derived from protein of human papilloma virus (HPV), wherein the amino acid sequence comprises a nonapeptide derived from protein E6 or E7 of HPV or HPV 18, and wherein the nonapeptide has the ability to bind in the grooves on top of the human major histocompactability complex (MHC) Class I molecule, as well as pharmaceutical compositions comprising this nonapeptide. These features are recited in the claims. As stated above, the basis for this invention is applicants' discovery of HLA class I binding peptides of HPV16 and HPV18 with CTL inducing properties. Schoolnik does not disclose peptides comprising the claimed sequences combined with the claimed features of the peptides. In addition, Schoolnik does not disclose peptides which bind to the MHC Class I molecule or that are cytotoxic to T lymphocyte epitopes. Schoolnik discloses peptides which would induce a B-cell response, not a CTL response. In fact, Schoolnik does not disclose <u>any</u> of the peptides claimed in the instant invention.

Moreover, as mentioned above, the subject invention provides for inducing an immune response through T-cell mediated immunity. No antibodies are contemplated in this invention, only peptides presented to MHC-I to elicit an immune response have been envisaged. Schoolnik merely discusses the raising of antibodies to viral proteins, but does not illicit an immune response. The antibodies raised would presumably be used as a therapy to HPV related diseases. The T-cell mediated response and the antibody response are separate and distinct types of immunity. Schoolnik does not address, contemplate or suggest the T-cell mediated immunity through the presentation of the claimed peptides by MHC-I to illicit an immune response as is claimed in the subject invention. Accordingly, applicants maintain that amended claims 2, 4, 7-8, 11, 13, 15-

16 and 25 define an invention patentable over the cited reference, and submit that the cited reference fails to set forth either a case of anticipation or a prima facie case of obviousness. The reference therefore cannot be said to anticipate or render obvious the claimed invention. In view of these remarks, applicants maintain that claims 2, 4, 7, 8, 11, 13, 15, 16 and 25 are patentable over Schoolnik, and that the rejections under 35 U.S.C. §102(b) and §103 should be withdrawn.

Conclusion

For the reasons set forth herein, applicants respectfully request that the Examiner reconsider and withdraw the rejections, and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Robert D. Katz Date
Reg. No. 30,141

Robert D. Katz, Esq.
Registration No. 30,141
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036
(212) 278-0400

Dkt. 45113/RDK/AG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Wybe Martin Kast et al.

Serial No. : 08/170,344 Examiner: N. Minnifield

Filed : March 30, 1994

For : PEPTIDES OF HUMAN PAPILLOMA VIRUS FOR USE IN HUMAN T CELL RESPONSE INDUCING COMPOSITIONS

1185 Avenue of the Americas
New York, NY 10036

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TERMINAL DISCLAIMER

Petitioner, Rijksuniversiteit Leiden, a state university organized and existing under the laws of the Netherlands, and engaged in business at Stationweg 46, 2312 AV Leiden, The Netherlands, the assignee of record of the entire right, title and interest in and to the above-identified application by virtue of an assignment from Wybe Martin Kast, Cornelis Joseph Maria Melief, Alessandro D. Sette and John C. Sidney, recorded with the United States Patent and Trademark Office on March 30, 1994 at reel 7001/frame0668, hereby disclaims the terminal portion of the statutory term of any patent granted on the subject application equivalent to the lesser of (a) the period of abandonment of the application, or (b) the period extending beyond twenty years from the date on which the application for the patent was filed in the United States or, if the application contains specific reference to an earlier filed application(s) under 35 U.S.C. §120, §121 or §365(c), from the date on which the earliest such application was filed. This disclaimer also applies to any patent granted on an application filed before June 8, 1995, that contains a specific reference under 35 U.S.C. §120, §121 or §365(c) to the

Exhibit M

above identified application. This disclaimer is binding upon the grantee, its successors or assigns.

I certify that I have reviewed the above-identified assignment and that, to the best of my knowledge and belief, Rijksuniversiteit Leiden has right, title and interest in and to the subject application. I further certify that I am authorized to sign this Terminal Disclaimer on behalf of Rijksuniversiteit Leiden.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Rijksuniversiteit Leiden

Date:_____ By:_____(signature)

_____(printed name)

SEED CAPITAL INVESTMENTS

ONTVANGEN
19 MEI 2004
AMERSFOORT

Vereenigde
T.a.v. de heer dr M.P.W. Einerhand
Snouckaertlaan 42
3811 MB AMERSFOORT

per fax: 033 422 7319
confirmation by post

S294.04d /Your ref. ME/P20884US00 / HPV-V US Patent Application No. 08/170,334
18 May 2004

Dear Mr. Einerhand,

We recently received your letter dated 29 April 2004, which included a proposal from Cooper & Dunham for reinstating the above application.

After consultation with our US partner we have come to the conclusion that the Petition to Withdraw the Holding of Abandonment in this case appears to be in order. Please request that Cooper & Dunham proceed. However, as mentioned on several previous occasions, please note that we that we are still waiting for a detailed explanation from Cooper & Dunham.

Please also be advised that SCI expects to be reimbursed for all expenses and any related costs (including damages) that have been incurred or will be incurred as a result of the abandonment of this application. We would also like to make it very clear that SCI will not pay or reimburse any expenses for the reinstatement of this US application to either Vereenigde or Cooper & Dunham. We kindly ask you to pass this message on to your US partner.

We would appreciate if you would keep us informed on all future developments.

Yours sincerely,
SEED CAPITAL INVESTMENTS (SCI) B.V.

W.J.M. de Vette
Director

P.O.Box 151
3720 AD Bilthoven
the Netherlands
Tel.+31 (0)30 295 5247

Prof. Bronkhorstlaan 26
3723 MB Bilthoven
the Netherlands
Fax.+31 (0)30 284 1628

Seed Capital Investments (SCI) B.V.
ABN-Amro Bank 46.40.13.795 KvK Utrecht 30091333
Seed Capital Investments-2 (SCI-2) B.V.
ABN-Amro Bank 46.25.38.660 KvK Utrecht 30128606

Exhibit N

Den Haag • Groningen • Arnhem • 's-Hertogenbosch • Amersfoort • Nijmegen

Patent Attorneys
Trademark Attorneys
Attorneys-at-Law

VEREENIGDE

BY FACSIMILE: +1 212 391 0525
Cooper & Dunham
1185 Avenue of the Americas
New York, N.Y. 10036
USA

Nieuwe Parklaan 97

P.O. Box 87930
2508 DH Den Haag
The Netherlands

Telephone +31 70 416 67 11
Telefax +31 70 416 67 99

e-mail patent@vereenigde.nl
trademark@vereenigde.nl
legal@vereenigde.nl

www.vereenigde.com

Your ref. 45113
Our ref. ME/P20884US00

Den Haag,
June 1, 2004

Re: U.S. patent application No. 08/170,344
in the name of Rijksuniversiteit Leiden

Dear dr. Katz,

The client has approved the draft petition to revive that you provided for their review. Please go forward and file the petition. The signing of the terminal disclaimer by the University will take some time. We will forward you the signed disclaimer upon receipt thereof by us. As discussed on the phone, you will file the petition with an unsigned disclaimer, together with a letter explaining that we will file the signed disclaimer as soon as we have the signatures.

On a different note, the client has requested that we forward a letter to you. The letter, of which a copy is herein enclosed, is self-explanatory.

Sincerely,
VEREENIGDE

M. Einerhand

Exhibit O

LEIDS UNIVERSITAIR MEDISCH CENTRUM

ONTVANGEN
30 JUN 2004
AMERSFOORT

afdeling Raad van Bestuur
postzone H-01-Q
Mw. Y. Bleeksma

telefoon 071 526 2704 fax 071 524 8125
e-mail y.bleeksma@lumc.nl
onze referentie 42164/
uw referentie ME/P20884US00

datum 29 juni 2004
onderwerp Terminal disclaimer inz. octrooiaanvraag

aan Verenigde
T.a.v. de heer M. Einerhand
adres Snouckaertlaan 42
3811 MB Amersfoort

Geachte heer Einerhand,

Bijgaand ontvangt u een getekend exemplaar van de Terminal Disclaimer inz. octrooiaanvraag in de VS nr. 08/170,344 'HPV-V' retour.

Met vriendelijke groet,

Mw. Y. Bleeksma
managementassistente

Bijlage(n): Getekend exemplaar Terminal Disclaimer

Exhibit P

Dkt. 45113/RDK/AG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Wybe Martin Kast et al.

Serial No. : 08/170,344 Examiner: N. Minnifield

Filed : March 30, 1994

For : PEPTIDES OF HUMAN PAPILLOMA VIRUS FOR USE IN HUMAN T CELL RESPONSE INDUCING COMPOSITIONS

1185 Avenue of the Americas
New York, NY 10036

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

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Petitioner, Rijksuniversiteit Leiden, a state university organized and existing under the laws of the Netherlands, and engaged in business at Stationweg 46, 2312 AV Leiden, The Netherlands, the assignee of record of the entire right, title and interest in and to the above-identified application by virtue of an assignment from Wybe Martin Kast, Cornelis Joseph Maria Melief, Alessandro D. Sette and John C. Sidney, recorded with the United States Patent and Trademark Office on March 30, 1994 at reel 7001/frame0668, hereby disclaims the terminal portion of the statutory term of any patent granted on the subject application equivalent to the lesser of (a) the period of abandonment of the application, or (b) the period extending beyond twenty years from the date on which the application for the patent was filed in the United States or, if the application contains specific reference to an earlier filed application(s) under 35 U.S.C. §120, §121 or §365(c), from the date on which the earliest such application was filed. This disclaimer also applies to any patent granted on an application filed before June 8, 1995, that contains a specific reference under 35 U.S.C. §120, §121 or §365(c) to the

above identified application. This disclaimer is binding upon the grantee, its successors or assigns.

I certify that I have reviewed the above-identified assignment and that, to the best of my knowledge and belief, Rijksuniversiteit Leiden has right, title and interest in and to the subject application. I further certify that I am authorized to sign this Terminal Disclaimer on behalf of Rijksuniversiteit Leiden.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Rijksuniversiteit Leiden

Date: 16 JUNE 2004

By: _____ (signature)

H.J. KLEIJMEER (printed name)

Den Haag • Groningen • Arnhem • 's-Hertogenbosch • Amersfoort • Nijmegen

Patent Attorneys
Trademark Attorneys
Attorneys-at-Law

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trademark@vereenigde.nl
legal@vereenigde.nl

www.vereenigde.com

BY FACSIMILE: +1 212 391 0525
Cooper & Dunham
1185 Avenue of the Americas
New York, N.Y. 10036
USA

Attn. Mr. Robert D. Katz

Your ref. 45113
Our ref. ME/P20884US00

Den Haag,
July 1, 2004

Re: U.S. patent application No. 08/170,344
in the name of Rijksuniversiteit Leiden

Dear Mr. Katz,

Thank you for your facsimile of June 23, 2004 in the matter of the above-identified patent application.

Please find enclosed the signed terminal disclaimer.

Should you have any questions or need additional information, please do not hesitate to contact me.

Very truly yours,
VEREENIGDE

M. Einerhand

Encl.: as mentioned

ne

Exhibit Q

Dkt. 45113/RDK/AG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Wybe Martin Kast et al.

Serial No. : 08/170,344 Examiner: N. Minnifield

Filed : March 30, 1994

For : PEPTIDES OF HUMAN PAPILLOMA VIRUS FOR USE IN HUMAN T CELL RESPONSE INDUCING COMPOSITIONS

1185 Avenue of the Americas
New York, NY 10036

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

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above identified application. This disclaimer is binding upon the grantee, its successors or assigns.

I certify that I have reviewed the above-identified assignment and that, to the best of my knowledge and belief, Rijksuniversiteit Leiden has right, title and interest in and to the subject application. I further certify that I am authorized to sign this Terminal Disclaimer on behalf of Rijksuniversiteit Leiden.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Rijksuniversiteit Leiden

Date: 16 June 1997

By: _____ (signature)

H.J. KOLLTVEER (printed name)

*** TRANSMISSIERAPPORT ***

PRINTTIJD 01.07.'04 12:27 ID:VEREENIGDE AMERSFOORT FAX:0334227319

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DOC. No.	START DATUM/TIJD	WIJZE	LOCATIE	OPGESL. PAGS.	VZ./OV. PAGS.	TOTALE DUUR	CODE
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Patent Attorneys
Trademark Attorneys
Attorneys-at-Law

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BY FACSIMILE: +1 212 391 0525
Cooper & Dunham
1185 Avenue of the Americas
New York, N.Y. 10036
USA

Attn. Mr. Robert D. Katz

Your ref. 45113
Our ref. ME/P20884US00

Den Haag,
July 1, 2004

Re: U.S. patent application No. 08/170,344
in the name of Rijksuniversiteit Leiden

Dear Mr. Katz,

Thank you for your facsimile of June 23, 2004 in the matter of the above-identified patent application.

Please find enclosed the signed terminal disclaimer.

Should you have any questions or need additional information, please do not hesitate to contact me.

Very truly yours,
VEREENIGDE

M. Einerhand

Encl.: as mentioned

ne.

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Shipper's reference (up to 32 characters but only first 12 will be shown on invoice): 1604894USU0

Company name: VEREFNIGDE

Address: SNOUCKAERTLAAN 42 AMERSFOORT THE NETHERLANDS

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3 To (Receiver)

Company name: Cooper & Dunham

Delivery address (DHL cannot deliver to a PO Box): 1185 Avenue of the Americas New York, NY 10036

Postcode/Zip Code (required): NY 10036

Country: USA

Contact person: Mr. Kirk Katz

Phone, Fax or E-mail (required): 1 212 3910525

4 Shipment details

Total number of packages	Total Weight	Pieces	Length	Width	Height
1	0.5 kg				

5 Full description of contents

Give content and quantity: documents

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Shipper's VAT/GST number

Receiver's VAT/GST or Shipper's EIN/SSN

Declared Value for Customs (as on commercial/proforma invoice)

Harmonised Commodity Code if applicable

TYPE OF EXPORT [ ] Permanent [ ] Repair / Return [ ] Temporary

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[ ] Receiver [ ] Shipper [ ] Other .... *specify approved account number*

7 Shipper's agreement (Signature required)

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Route No.

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EXHIBIT 1

Overview of details regarding the status overview of family EP Pat. No. 0 593 754 / PCT/NL93/00093 in the name of Rijksuniversiteit Leiden, as of August 17, 2004

Family : inventor(s)	Owner (Licensee)	Countries	Application /patent No.	Filing Date (Priority Date)	Status Grant Date
HPV-V :Kast, Wybe Martin Melief, Cornelis Joseph Maria Sette, Alessandro D. Sidney, John C.	Rijks-universiteit Leiden	AU	675794	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	30-12-1996
		CA	2,112,798	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	Pending
		IL	105554	29-04-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	18-11-1999
		JP	5-519145	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	Pending
		MX	213898	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	25-04-2003
		NZ	253330	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	09-10-1996
		US	08/170,344	04-05-1193 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	abandoned, re-instatement initiated
		ZA	93/3135	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	29-04-1994

		ATEP	E207495	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	24-10-2001
		BEEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	24-10-2001
		CHEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		DEEP	69330988.1	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		DKEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		EP00	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		ESEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		FREP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		GBEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		GREP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001

		IEEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		ITEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		LUEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		MCEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		NLEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		PTEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001
		SEEP	0593754	04-05-1993 (05-05-1992) (10-12-1992) (01-02-1993) (05-03-1993)	12-10-2001